New Perspectives in Oxazole Chemistry. 2.[1] One-Pot Efficient Access to Polyfunctionalized Nitroenamines by Nucleophilic Ring Opening of 4-Nitro Derivatives

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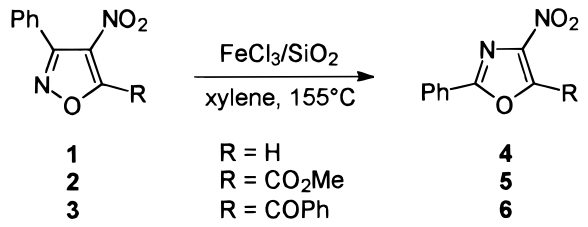
Introduction

The use of heterocycles in organic synthesis has impressively grown over the past decades,[2] and in this respect, aromatic oxazoles emerged as excellent synthons in diverse standard protocols.[3] Valuable heterodienes for the preparation of pyridine and furan products with alkenes and alkynes, respectively,[4] they were also widely employed as masked acylating agents for the build-up of macrocyclic lactones, through the oxazole-triamide rearrangement with singlet oxygen.[5]

After a systematic investigation on the cycloaddition chemistry of 4-nitroisoxazoles,[6] we more recently focused our attention on the corresponding oxazoles, and obtainment of the 4-nitro-2-phenyl derivative **4** paved the way for an evaluation of the synthetic potentialities of this unexplored system. Although a remarkable activation of the C(4)═C(5) double bond by the NO_2 group enabled **4** to enter as a very reactive partner into hitherto unknown, normal [2 + 4] cycloadditions with several 4π counterparts, a quite different reaction course was observed with 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil, involving a polyfunctionalized nitroalkene as key intermediate.[1]

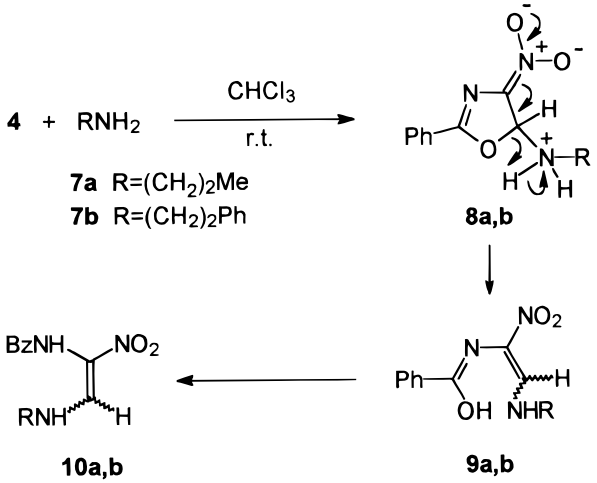
In light of this finding and bearing in mind the role of nitroenamines in both theoretical and synthetic studies,[7] we decided to gain better insight into the possibility of exploiting the same system as a source of the title compounds with primary and secondary amines.

Scheme 1



1 R = H **4**
2 R = CO_2Me **5**
3 R = COPh **6**

Scheme 2



Results and Discussion

Since conversion of 4-nitro-3-phenylisoxazole (**1**) into **4** with a trace amount of concentrated HCl in xylene at 155 °C suffered from a modest absolute yield (29%) and recycling of the unreacted starting material rested on a tedious chromatographic workup,[1] we repeatedly tried to improve this procedure.

When thermolysis was carried out under the same conditions but the above catalyst was replaced with the anhydrous $FeCl_3$−SiO_2 reagent, previously employed as an effective Lewis acid for different purposes,[8] compound **1** completely disappeared after 35 h and the desired product **4** was easily isolated in 42% yield; furthermore, we succeeded in this way in obtaining for the first time in reasonable yields (54% and 44%) the difunctionalized nitrooxazoles **5** and **6** from the corresponding isomers **2** and **3**, respectively (Scheme 1).

Treatment of **4** with a very small excess of propylamine (**7a**) and phenethylamine (**7b**) in chloroform at room temperature afforded almost quantitatively the nitroenamines **10a** and **10b** through a nucleophilic attack at position 5, followed by ring cleavage of the resulting dipolar oxazolines **8a** and **8b**, respectively (Scheme 2).

While compounds **5** and **6** gave complex mixtures of inseparable products with the same reagents, very clean reactions of the three nitrooxazoles **4**−**6** with pyrrolidine (**11a**) allowed us to isolate the enamines **12**−**14** in 97−98% yields (Scheme 3); noteworthily, a total selectivity was now observed for the interaction of **11a** on the

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(2) (a) Kozikowski, A. P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 1, Chapter 16. (b) Lipschutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Ho, T.-L. *Symmetry: A Basis for Synthesis Design*; Wiley: New York, 1995; Chapter 9.

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(8) For a few typical examples, see: (a) Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 413. (b) Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 1267. (c) Fadel. A.; Yefsah, R.; Salaün, J. *Synthesis* **1987**, 37.

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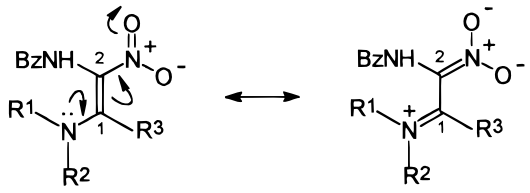
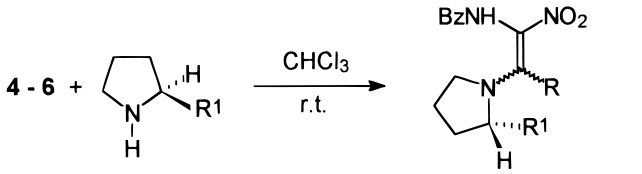


Figure 1.

Scheme 3



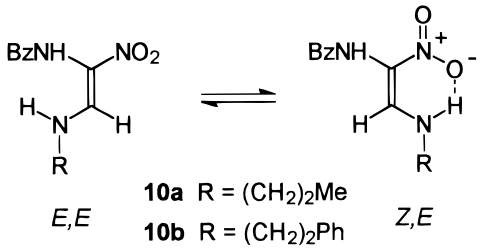
11a R^1=H
11b R^1=CH_2OMe

12 R=R^1=H
13 R=CO_2Me, R^1=H
14 R=COPh, R^1=H
15 R=H, R^1=CH_2OMe
16 R=CO_2Me, R^1=CH_2OMe
17 R=COPh, R^1=CH_2OMe

remarkably electrophilic C-5 ring carbon of the nitroester **5**. The growing interest in chiral nitroenamines as attractive substrates for enantioselective reactions[9] prompted us to test the reactivity of the above oxazoles toward (*S*)-2-methoxymethylpyrrolidine (SMP) (**11b**); these reactions, too, gave very satisfactory results and the desired products **15**−**17** were obtained in excellent yields (Scheme 3).

The structures of the new nitro compounds **5**, **6**, **10a**,**b**, and **12**−**17** were determined from analytical and spectral evidence (Experimental Section). Particularly, upon going from **4**−**6** to the open-chain derivatives, the IR NO_2 stretching vibrations at 1530−1570 and 1360−1374 cm^{-1} were replaced by strong absorptions at 1208−1261 cm^{-1} for the nitronate moiety;[10] in addition, whereas the IR patterns of the latter were also characterized by the "enamine band" at 1570−1655 cm^{-1}, the corresponding ^{13}C NMR spectra showed resonances at δ 115.2−118.6 for the C-2 carbons, strongly shielded by the push−pull electron drift (Figure 1).

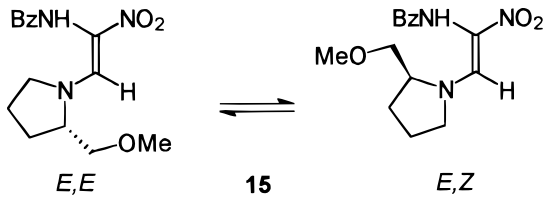
The stereochemical behavior of the nitroenamines, inferred from their ^1H and ^{13}C NMR spectra, was notably influenced by the nature of the substituents at position 1. Compounds **10a**,**b**, containing a secondary amino group, were shown to exist as mixtures of *E*,*E* and *Z*,*E* isomers (Figure 2),[11] whose proportions (ca. 5:1) were deduced from the relative intensities of the amide NH singlets at δ 9.57−9.80; on the other hand, while the predominant forms are characterized by doublets at δ 8.50 and 8.43, respectively, for the more deshielded H-1 protons,[12] the corresponding signals of the minor ones were evidenced at lower frequencies (δ 7.55 and 7.57) by HETCOR experiments with the C-1 resonances at δ 146.8−149.0. With regard to the pyrrolidino enamines, partial duplications of NMR signals were only observed



10a R = $(CH_2)_2Me$
10b R = $(CH_2)_2Ph$

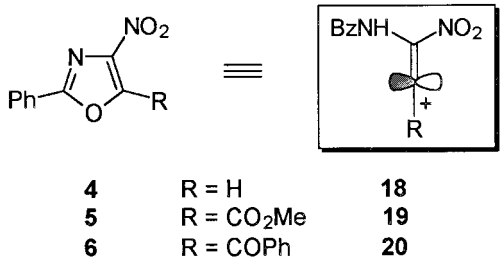
E,*E* *Z*,*E*

Figure 2.



E,*E* **15** *E*,*Z*

Figure 3.



4 R = H **18**
5 R = CO_2Me **19**
6 R = COPh **20**

Figure 4.

for the most crowded benzoyl derivative **14**, involving both *E* and *Z* isomers; the *E* configuration, firmly established for **12** on the basis of the diagnostic[12] H-1 value (δ = 8.66) also appeared to be preferred for the nitro ester **13**, better ensuring an effective delocalization between amino and nitro groups.

Replacement of pyrrolidine with the asymmetrical SMP well accounts for the existence of compound **15** in two forms (ca. 50%) arising from a common *E* configuration with different conformations around the C(1)−N bond (Figure 3), as supported by the presence of two singlets of comparable intensities at δ 8.62 and 8.65 for the olefinic proton. Whereas a conformational equilibrium between similar forms can be also taken into consideration for the ester **16**, giving rise to a severe broadening for some ^1H and ^{13}C resonances, the presence of both *E* and *Z* configurations for **17** is strongly suggested by its ^{13}C NMR pattern showing well-resolved triads of signals for different carbons (Experimental Section).

In conclusion, a satisfactory preparation has been accomplished for the 4-nitrooxazoles **4**−**6** that can be regarded as attractive synthetic equivalents of the nitrovinyl cations **18**−**20** (Figure 4), for a new simple and efficient access to polyfunctionalized nitroenamine systems by ring opening with amine nucleophiles.

Experimental Section[13]

Thermal Isomerization of the Nitroisoxazoles 1−3 into the Oxazoles 4−6. General Procedure. A mixture of the

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(10) Reference 7b, p 220.
(11) The symbols indicate, in the order shown, the "configuration" around the C(1)═C(2) double bond and the "conformation" around the C(1)−N single bond.
(12) Ostercamp, D. L.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1021.
(13) Instruments and general techniques are described in ref 1. The NMR spectra of the nitrooxazoles and nitroenamines were recorded in $CDCl_3$ and DMSO-d_6 solutions, respectively. The values in square brackets refer to the most evident resonances of the minor isomer(s).

nitroisoxazole (1 mmol) and the anhydrous $FeCl_3-SiO_2$ reagent[8a] (0.010 g) in xylene (3 mL) was stirred in a screw-capped tube (Pyrex N. 18) at 155 °C until the starting material disappeared (TLC, ^{1}H NMR). After dilution with dichloromethane (5 mL) and removal of the catalyst by filtration, the residue left by evaporation to dryness was subjected to flash chromatography with petroleum ether/ethyl acetate (10:1 v/v) as eluent.

A. The reaction product from the thermolysis of **1** (35 h) gave compound **4** (R_f = 0.32, 0.080 g, 42%), identical with a specimen previously described.[1]

B. Chromatographic workup of the crude product from **2** (38 h) afforded methyl 4-nitro-2-phenyloxazole-5-carboxylate (**5**) (R_f = 0.25, 0.135 g, 54%) that was crystallized from ether as yellow needles: mp 139−140 °C; IR 1739, 1534, and 1366 cm^{-1}; ^{1}H NMR δ 4.03 (s, 3H), 7.48−7.61 (m, 3H), 8.13−8.18 (m, 2H); ^{13}C NMR δ 53.4 (q), 124.3 (s), 127.6 (d), 129.1 (d), 133.05 (d), 134.9 (s), 148.5 (s), 155.5 (s), 160.9 (s). Anal. calcd for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Found: C, 53.46; H, 3.32; N, 11.33.

C. The residue from **3** (48 h) yielded 5-benzoyl-4-nitro-2-phenyloxazole (**6**) as a pale yellow solid (R_f = 0.35, 0.130 g, 44%): mp 133−134 °C (from ethanol); IR 1661, 1523, and 1372 cm^{-1}; ^{1}H NMR δ 7.42−7.78 (m, 6H), 7.92−7.98 (m, 2H), 8.12−8.19 (m, 2H); ^{13}C NMR δ 124.5 (s), 127.5 (d), 129.1 (d), 129.2 (d), 129.5 (d), 132.9 (d), 134.9 (s), 135.0 (d), 142.5 (s), 147.3 (s), 160.6 (s), 181.2 (s). Anal. calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.56; H, 3.50; N, 9.42.

Synthesis of the Nitroenamines 10a,b and 12−17. General Procedure. A mixture of the nitrooxazole (0.5 mmol) and the amine (0.51 mmol) in chloroform (1.5 mL) was stirred at room temperature in a screw-capped tube (Pyrex N. 13) for 24 h. The residue left by removal of the solvent and prolonged evacuation under reduced pressure was taken up in *n*-pentane, filtered, and dried.

A. Treatment of **4** with propylamine (**7a**) (0.030 g, 0.042 mL) afforded 2-benzoylamino-2-nitro-1-propylaminoethylene (**10a**) as yellow flakes (0.124 g, 99%): mp 131−132 °C dec (from dichloromethane); IR 3243, 1678, 1655, and 1208 cm^{-1}; ^{1}H NMR δ 0.88 (t, J = 7.3 Hz), [0.90 (t, J = 7.3 Hz)], 1.45−1.70 (m), 3.20−3.43 (m), 7.42−7.68 (m), 7.85−8.25 (m), 8.50 (d, J = 14.0 Hz), 9.45−9.58 (br m), 9.60 (s), [9.80 (s)]; ^{13}C NMR δ 10.9 (q), 23.8 (t), 50.2 (t), [50.8 (t)], [115.2 (s)], 118.4 (s), 127.9 (d), 128.3 (d), 128.4 (d), 128.7 (d), 132.0 (d), 132.2 (d), 133.6 (s), 133.85 (s), 147.15 (d), [149.0 (d)], 165.9 (s), [167.2 (s)]. Anal. calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.56; H, 6.13; N, 16.77.

B. Reaction of **4** with phenethylamine (**7b**) (0.062 g, 0.064 mL) gave 2-benzoylamino-2-nitro-1-(2-phenylethylamino)ethylene (**10b**) (0.154 g, 99%) that was crystallized from ethanol as pale yellow needles: mp 124−125 °C; IR 3275, 1676, 1648, and 1210 cm^{-1}; ^{1}H NMR δ 2.81 (t, J = 7.4 Hz), [2.92 (t, J = 7.4 Hz)], 3.43−3.70 (m), 7.18−7.38 (m), 7.42−7.65 (m), 7.90−8.05 (m), 8.08−8.22 (br m), 8.43 (d, J = 14.9 Hz), 9.57 (s), [9.75 (s)]; ^{13}C NMR δ [36.6 (t)], 36.8 (t), 49.8 (t), [50.3 (t)], [115.2 (s)], 118.3 (s), 126.4 (d), 127.7 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.9 (d), 129.0 (d), 129.3 (d), 131.9 (d), 132.0 (d), 133.4 (s), 133.6 (s), 138.3 (s), 138.4 (s), 146.8 (d), [148.5 (d)], 165.9 (s), [167.1 (s)]. Anal. calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.39; H, 5.55; N, 13.76.

C. Ring opening of **4** with pyrrolidine (**11a**) (0.036 g, 0.042 mL) yielded (*E*)-2-benzoylamino-2-nitro-1-(pyrrolidin-1-yl)ethylene (**12**) as a yellow solid (0.128 g, 98%): mp 179 °C dec (from acetone); IR 3310, 1672, 1634, 1256, and 1217 cm^{-1}; ^{1}H NMR δ 1.72−1.97 (m, 4H), 3.14−3.36 (m, 1H), 3.54−3.76 (m, 3H), 7.50−7.68 (m, 3H), 7.92−7.99 (m, 2H), 8.66 (s, 1H), 9.81 (s, 1H); ^{13}C NMR δ 24.1 (t), 25.5 (t), 47.4 (t), 54.9 (t), 118.2 (s), 128.0 (d), 128.9 (d), 132.4 (d), 133.4 (s), 143.5 (d), 167.3 (s). Anal. calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.41; H, 5.76; N, 16.37.

D. Reaction of **5** with **11a** gave (*E*)-methyl 3-benzoylamino-3-nitro-2-(pyrrolidin-1-yl)acrylate (**13**) (0.155 g, 97%) that was crystallized from ether as yellow needles: mp 148−149 °C; IR 3341, 1746, 1667, 1586, and 1252 cm^{-1}; ^{1}H NMR δ 1.80−1.92 (m, 4H), 3.25−3.46 (br m, 2H), 3.52−3.74 (br m, 2H), 3.89 (s, 3H), 7.50−7.70 (m, 3H), 7.93−8.02 (m, 2H), 10.05 (s, 1H); ^{13}C NMR δ 24.8 (sbr t), 50.9 (sbr t), 53.5 (q), 117.7 (s), 128.1 (d), 129.0 (d), 132.6 (d), 133.0 (s), 147.7 (s), 162.7 (s), 167.1 (s). Anal. calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.38; H, 5.60; N, 12.87.

E. Treatment of **6** with **11a** afforded 1-benzoyl-2-benzoylamino-2-nitro-1-(pyrrolidin-1-yl)ethylene (**14**) (0.179 g, 98%): an analytical sample, obtained as ivory-colored needles by crystallization from acetone, gradually darkened above 185 °C and melted with decomposition at 198 °C; IR 3314, 1665, 1578, and 1261 cm^{-1}; ^{1}H NMR δ 1.80−1.98 (vbr s), 3.0−3.18 (vbr s), 3.30−3.55 (vbr m), 3.78−3.98 (vbr s), 7.55−7.78 (m), 7.98−8.08 (m), 8.25−8.33 (m), [10.18 (sbr s)], 10.24 (sbr s); ^{13}C NMR δ 24.8 (br t), 51.2 (br t), 118.4 (s), [118.6 (s)], 127.8 (d), 128.0 (d), 128.2 (d), 128.25 (d), 129.0 (d), 129.6 (d), 132.6 (d), 132.7 (d), 132.8 (s), 133.1 (s), 134.3 (d), 134.4 (d), 134.45 (s), 134.6 (s), [153.3 (s)], 153.45 (s), [167.0 (s)], 167.3 (s), [186.2 (s)], 186.7 (s). Anal. calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.50; H, 5.30; N, 11.60.

F. Reaction of **4** with SMP (**11b**) (0.059 g, 0.063 mL) gave (*E*)-2-benzoylamino-1-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2-nitroethylene (**15**) (0.148 g, 97%) that was crystallized from ethyl acetate as pale yellow needles: mp 138−139 °C dec; $[\alpha]^{29}_D$ = (−)12.1 (*c* 0.925, $CHCl_3$); IR 3277, 1661, 1632, and 1269 cm^{-1}; ^{1}H NMR δ 1.57−1.75 (br m), 1.78−2.02 (br m), 3.22−3.55 (br m), 3.32 (s), [3.34 (s)], 3.60−3.78 (br m), 4.03−4.18 (br m), 7.45−7.65 (m), 7.90−7.98 (m), 8.62 (s), [8.65 (s)], [9.78 (sbr s)], 9.81 (sbr s); ^{13}C NMR δ 23.7 (t), 26.4 (t), [26.6 (t)], 47.7 (t), [48.1 (t)], 58.7 (d), 63.8 (q), 74.3 (t), [74.5 (t)], 118.6 (s), 128.0 (d), 128.8 (d), 132.3 (d), 133.4 (s), 143.1 (d), [166.8 (s)], 167.7 (s). Anal. calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.83; H, 6.27; N, 14.10.

G. Ring cleavage of **5** with **11b** yielded (*E*)-methyl 3-benzoylamino-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-3-nitroacrylate (**16**) as a yellow solid (0.174 g, 96%): an analytical sample, obtained by crystallization from *n*-pentane/ether, wrinkled above 70 °C and melted at 90−91 °C; $[\alpha]^{21}_D$ = (−)68.4 (*c* 1.85, $CHCl_3$); IR 3296, 1741, 1666, 1579, and 1268 cm^{-1}; ^{1}H NMR δ 1.75−2.08 (br m, 4H), 3.15−3.70 (br m, 4H), 3.42 (sbr s, 3H), 3.87 (sbr s, 3H), 3.95−4.30 (vbr s, 1H), 7.55−7.70 (m, 3H), 7.97−8.02 (m, 2H), 10.16 (br s, 1H); ^{13}C NMR δ 22.7 (sbr t), 27.7 (sbr t), 51.6 (sbr t), 53.4 (q), 58.6 (sbr q), 60.3 (sbr d), 73.4 (vbr t), 119.0 (vbr s), 128.0 (d), 128.8 (d), 132.5 (d), 132.9 (s), 146.8 (br s), 162.6 (s), 166.9 (vbr s). Anal. calcd for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83; N, 11.56. Found: C, 55.94; H, 6.01; N, 11.84.

H. Treatment of **6** with **11b** afforded 1-benzoyl-2-benzoylammino-1-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2-nitroethylene (**17**) (0.200 g, 98%) that was crystallized from *n*-pentane/ether as yellow needles: it gradually wrinkled above 90 °C and melted at 108−109 °C; $[\alpha]^{22}_D$ = (+)44.5 (*c* 1.05, $CHCl_3$); IR 3301, 1681, 1573, and 1254 cm^{-1}; ^{1}H NMR δ 1.70−1.98 (vbr m), 2.70−3.70 (vbr m), 4.02−4.15 (br m), 7.52−7.78 (sbr m), 7.90−8.10 (sbr m), 8.35−8.42 (br m), [10.15 (sbr s)], 10.30 (sbr s); ^{13}C NMR δ 22.1 (t), [22.3 (t)], [22.7 (t)], 27.4 (br t), [51.7 (sbr t)], 52.3 (t), [58.0 (q)], [58.4 (q)], 58.7 (q), 60.0 (br d), 72.3 (vbr t), [118.6 (s)], 119.1 (s), 127.7 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.85 (d), 128.9 (d), 129.3 (d), 129.6 (d), 132.6 (d), 132.7 (d), 132.9 (s), 133.1 (s), 133.3 (s), 134.2 (d), 134.7 (s), 152.8 (br s), 166.3 (vbr s), [185.8 (s)], [186.3 (s)], 186.9 (s). Anal. calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.46; H, 5.68; N, 10.47.

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