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Condensed 2-pyrrolidinone-1,2-oxazines from lithium enolate of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid and β-aryl, β-nitroenamines

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Abstract—The reaction of the lithium enolate of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid **3** with a series of β-aryl, β-nitroenamines unexpectedly afforded 6-aryl-2-benzyl-4-oxa-1-oxo-3a-methoxycarbonyl-2,5-diazaindenes **9a–d**, whose structure was determined by analytical and NMR spectroscopical analysis. The structure of **9b** was further confirmed by X-ray analysis. A reasonable mechanism for their formation is given.

1. Introduction

The γ-lactam nucleus (2-pyrrolidinone) characterizes several compounds with biological and pharmaceutical activities.[1] Furthermore, 2-pyrrolidinones are also useful intermediates in organic synthesis.[2] In particular, polyfunctionalized γ-lactams have been synthesized to obtain γ-aminobutyric acid (GABA) analogues by hydrolysis under either acidic or basic conditions.[3] GABA[4] is a major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and several psychiatric and neurological diseases are correlated with a disfunctioning of the GABA system, which acts in opposition to excitatory systems such as glutamate.[5] Many unnatural γ-amino acids have been designed for their promising therapeutic use in the treatment of these diseases, acting either as specific agonists at post-synaptic $GABA_A$ receptors[6] or as inhibitors of the GABA-uptake mechanism.[7] Within the frame of our research in the field of γ-lactams bearing a β-carboxylic group (such as **1**,[8] i.e., the aza analogue of paraconic acid **2**[9]), (Fig. 1) we have examined the reactivity of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid (**3**)[8b] with a series of β-aryl, β-nitroenamines (**4a–e**),[10] under strongly basic conditions, with the aim of obtaining new α-functionalized aza paraconic acid derivatives.

As a matter of fact, β-nitroenamines[11] react under strongly basic conditions with ketones, esters, and lactones **5** containing active hydrogens at the α-position to give the corresponding 2-*aci*-nitroalkylidene derivatives **6** as a consequence of a conjugative addition–elimination reaction (Scheme 1).[12]

The fate of these intermediates depends on the structure of both the substrate and the nitroenamine as well as on the type of the final treatment. With ketones,[12a] linear esters,[12b] and lactones the corresponding 1,4-dicarbonyl compounds **7** were isolated (for R^3=Me), as a result of a Nef reaction,[12a,13] while by treatment with a suitable alkylating reagent nitronic

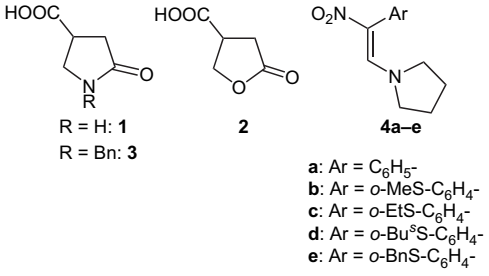

Figure 1. Reactants **3** and **4a–e**.

Keywords: γ-Lactams; β-Nitroenamines; Michael addition; Intramolecular redox process; Electrocyclic reaction; Condensed 1,2-oxazines.
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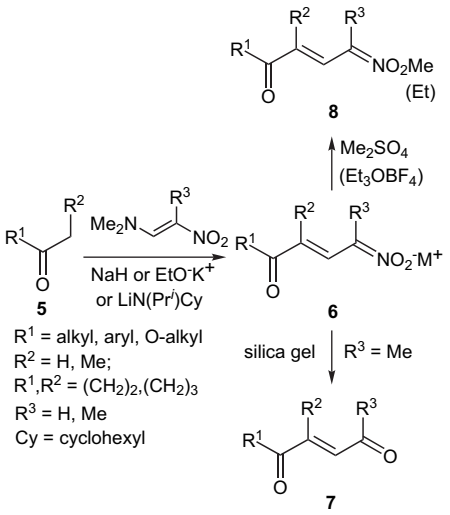
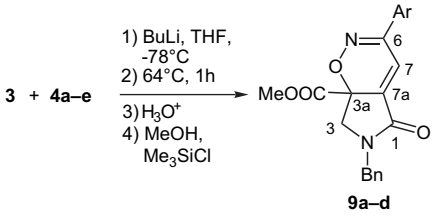


Scheme 1. General reactivity of carbonyl compounds and acidic derivatives with nitroenamines.

alkyl esters of the type **8** were the products, which could undergo further transformations.

2. Results and discussion

Lactamic acid **3** (twofold excess) in THF was treated with LDA (or *n*-butyllithium) (2.2–2.5 molar ratio with respect to **3**) under an inert atmosphere, at −78 °C. The β-nitroenamines **4a–e** were then added and the mixture was heated for 1 h. The crude reaction mixtures were acidified to pH 2 and subsequently esterified with methanol, in the presence of trimethylchlorosilane,[14] in order to separate esters **9a–d** from the methyl ester of substrate **3** (Scheme 2). No other products were detected.



Scheme 2. Formation of the 1,2-oxazine derivatives **9a–d**.

The structures of compounds **9a–d** were attributed on the basis of ^{1}H and ^{13}C NMR spectra, as well as by HRMS data, and definitively confirmed by a single crystal X-ray crystallographic analysis performed on 1,2-oxazine **9b** (Fig. 2).[15]

^{1}H and ^{13}C NMR spectra of compounds **9a–d** show very strict resemblances, in particular for protons and carbon atoms of the heterocyclic skeleton. The variations range within 0.3 ppm for protons and within less than 4 ppm for carbons (Table 1).

In the reaction of chiral racemic β-nitroenamine **4d**, the resulting product **9d** was about 1:1 mixture of two diastereomers, which could not be separated. Strangely enough, the β-nitroenamine **4e**, whose aromatic ring contains the *ortho*-benzylthio group, was found unreactive, probably due to steric reasons, allowing the complete recovery of the reagents.

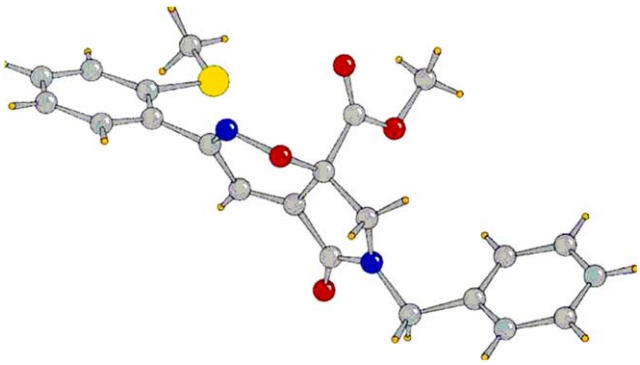


Figure 2. X-ray crystal structure of the 1,2-oxazine derivative **9b**.

Table 1. The main NMR spectroscopic data for compounds **9a–d**

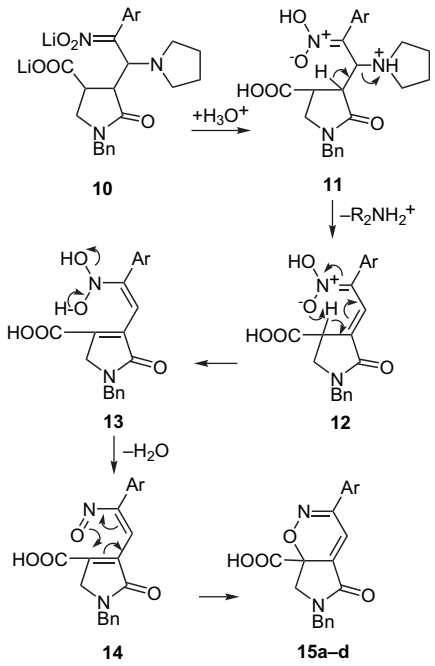
Compd	H-3	H-7	C-3	C-3a	C-6	C-7
9a	3.60, 3.80	7.07	46.8	74.4	155.0	112.0
9b	3.60, 3.82	6.83	46.6	74.4	156.4	115.1
9c	3.60, 3.81	6.81	46.5	74.2	156.7	115.2
9d (two diast.)	3.59, 3.81	6.81, 6.83	46.6	74.3	156.8, 156.9	115.62, 115.57

Compounds **9a–d** are unknown in the literature as yet. In fact, formations of 6*H*-1,2-oxazine derivatives are reported to proceed by a hetero Diels–Alder reaction of suitable alkenes with α-nitroso alkenes.[16,17] α-Nitro alkenes are known to give smoothly 1,2-oxazine-*N*-oxide derivatives in their reactions with enamines,[18] whereas silyl enol ethers, vinyl ethers, and isolated dienes react only in the presence of Lewis acid promoters.[19,20,21]

In order to gain information on the mechanism of the reaction observed, several attempts have been made to isolate at least one of the possible intermediates. To this purpose, the reaction work-up was performed with acids weaker than mineral acids and attempts to trap the expected nitronate intermediate of the type **6** (Scheme 1) with ethyl acrylate[22] and ethylidene malonate[22] were also made, but unsuccessfully. Anyway, on the basis of the expected reactivity of the reagents, the mechanism reported in Scheme 3 is proposed to account for the formation of these unusual bicyclic 1,2-oxazine derivatives **9a–d**.

As a matter of fact, we can assume that the lithium enolate of **3** adds to the β-nitroenamines **4** by the usual 1,4-conjugate Michael addition to give nitronate salt **10**. By acidification to pH 2, i.e., under the conditions of Nef reaction,[13] **10** gives **11**, which converts into **12** via the usual acid-catalyzed elimination of the secondary amine.

The *E*-configuration of the carbon–carbon double bond in **12** is necessary for the subsequent reaction steps. In fact, a fast cascade reaction can conceivably occur due to the simultaneous presence of the allylic proton and oxidizing nitronic acid function,[23] suitably positioned for an intramolecular



Scheme 3. Proposed mechanism of formation of the acidic forms **15a–d** of the 1,2-oxazine derivatives **9a–d**.

redox process. The resulting intermediate **13** would in turn lose a molecule of water from the $-N(OH)_2$ grouping, thus forming **14**. Finally, a 6π-thermal electrocyclization, involving the 1-nitroso-1,3-butadiene system[24,25] would afford the acids **15a–d**, isolated as their respective methyl esters **9a–d**. As to the intermediate **14**, very little is known about aliphatic nitrosodienes.[24] However, recent computational studies carried out on the cyclization pathways of 1-nitroso-1,3-butadiene[25] indicate that, although, 1,5-electrocyclization leading to pyrrole derivative is thermodynamically more favored than the 1,6-electrocyclization giving the 6*H*-1,2-oxazine, formation of this latter system is slightly faster than that of the former one.

3. Conclusions

The peculiar reactivity of the arylated β-nitroenamines **4** with the lithium enolate of the lactamic acid **3** leads to the heterocyclic derivatives **9**, which are to the best of our knowledge, the first examples of aza paraconic acid derivatives condensed with a six-membered heterocyclic ring. The key step in the reaction is likely to be the formation of the intermediate **12** of the proposed mechanism, from which the α-butenolides **13** and **14** are produced, thus allowing the heterodiene with an intramolecular inverse electron demand Diels–Alder reaction to occur.

4. Experimental

4.1. General

Melting points were measured using a Büchi 510 apparatus and were uncorrected. IR spectra were recorded for neat samples and for $CHCl_3$ solutions on a Jasco FTIR 200 spectrophotometer. ^1H and ^{13}C NMR spectra were run on either a 300 MHz Varian Inova 300 instrument or a Jeol EX-400 spectrometer (400 MHz for proton), using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Coupling constants are given in hertz. Mass spectra were recorded on a VG 7070 (70 eV) spectrometer. HRMS spectra were performed on a Finnigan MAT95XP spectrometer. TLC analyses were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluant: dichloromethane–ethyl acetate). Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). THF was distilled over benzophenone ketyl before each use.

Reagents: 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid **3** was prepared in accordance with the literature.[26] Analytical and spectroscopic data for (*S*)-(+)-**3** are given in Ref. 8b.

β-Nitroenamines **4a**[10a] and **4b**[10b] were synthesized according to the literature. Compounds **4c–e** were obtained following the synthetic procedure used for **4b**;[10c] the silver salt derived from the ring-opening of 3-nitrobenzo[*b*]thiophene[27] has been treated with a large excess of ethyl iodide, 2-iodobutane, and benzyl bromide, respectively.

4.1.1. (1*E*,3*Z*)-Ethylthio-2-nitro-1-pyrrolidino-1,3-butadiene (4c). Yield 42%; yellow solid; mp 112–113 °C; IR ($CHCl_3$) 1617, 1487, 1457, 1400, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (1H, t, J=7.5 Hz), 1.82 (4H, br band), 2.71 (2H, br band), 2.93 (2H, q, J=7.5 Hz), 3.66 (2H, br band), 7.12–7.19 (1H, m), 7.24–7.30 (2H, m), 7.32–7.39 (1H, m), 8.67 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 24.3, 25.9, 26.2, 47.9, 55.0, 122.5, 125.8, 129.5, 130.9, 133.5, 140.8, 145.9; ESIMS, *m/z* 301.0 $[M+Na]^+$; MS (70 eV) *m/z* 278 (4), 232 (12), 216 (22), 203 (14), 163 (59), 148 (30), 135 (100), 108 (16), 99 (17); HRMS (EI) calcd for $C_{14}H_{18}N_2O_2S$ (M^+): 278.1084; found: 278.1086.

4.1.2. (1*E*,3*Z*)-*sec*-Butylthio-2-nitro-1-pyrrolidino-1,3-butadiene (4d). Yield 12%; yellow oil; IR (film) 1618, 1487, 1455, 1399, 1256, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94–1.04 (m, 3H), 1.28 (3H, d, J=6.6 Hz), 1.46–1.73 (2H, m), 1.81 (4H, br band), 2.67 (2H, br band), 3.25 (1H, m), 3.66 (2H, br band), 7.14–7.40 (4H, m), 8.66 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 20.1, 20.4, 24.2, 25.8, 29.2, 29.3, 43.1, 48.0, 54.9, 122.7, 124.8, 124.9, 127.9, 128.3, 129.28, 129.32, 132.1, 132.3, 133.45, 133.52, 139.8, 140.1, 145.8; ESIMS *m/z* 328.9 $[M+Na]^+$; MS (70 eV) *m/z* 306 (1), 260 (10), 217 (21), 191 (11), 163 (5), 147 (8), 135 (100), 121 (6), 108 (5), 99 (7). HRMS (EI) calcd for $C_{16}H_{22}N_2O_2S$ (M^+): 306.1400; found: 306.1402.

4.1.3. (1*E*,3*Z*)-Benzylthio-2-nitro-1-pyrrolidino-1,3-butadiene (4e). Yield 27%; yellow solid; mp 128–129 °C; IR ($CHCl_3$) 1616, 1487, 1456, 1399, 1256, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (4H, br band), 2.54 (2H, br band), 3.63 (2H, br band), 4.12 (2H, m), 7.14–7.38 (9H, m), 8.65 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.7, 37.0, 47.9, 54.9, 122.2, 124.8, 126.7, 127.0, 128.2, 128.7, 129.3, 131.2, 133.2, 136.8, 140.1, 145.6;

Found: C ESIMS *m/z* 363.0 [M+Na]$^+$; MS (70 eV) *m/z* 294 (11), 225 (22), 134 (14), 91 (100), 65 (13); HRMS (EI) calcd for $C_{19}H_{20}N_2O_2S$ (M^+): 340.1247; found: 340.1247.

4.2. Reactions between lactamic acid 3 and nitroenamines 4a–d

4.2.1. General procedure. A solution of lithium diisopropylamide (2.5 mmol) in THF (3.5 mL) [or a solution of *sec*-butyllithium (2.2 mmol) in cyclohexane] was slowly added to a solution of **3** (1 mmol) in THF (23 mL), at −78 °C, under argon. The reaction mixture was stirred at −78 °C for 3 or 4 h, then it was slowly added to a solution of the appropriate nitroenamine **4** (0.5 mmol) in THF (2 mL) at the same temperature, by means of a double-ended needle. The mixture was gradually warmed to room temperature and then heated to reflux for 1 h. After cooling to room temperature, the mixture was further stirred overnight. The reaction mixture was quenched by the addition of 3 M HCl. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, the aqueous phase was acidified to pH 2 with 3 M HCl solution, and extracted three times with CH_2Cl_2. The combined organic layers were dried on anhydrous Na_2SO_4 and the solvent was removed to give the crude product (200–220 mg). This was esterified with methanol in trimethylchlorosilane and purified by flash column chromatography (silica gel, eluent: ethyl acetate–dichloromethane, gradient from 0% up to 10%) to afford **9a–d** as white crystalline solids in yields varying from 26 to 47%.

4.2.1.1. 2-Benzyl-3a-methoxycarbonyl-4-oxa-1-oxo-6-phenyl-2,5-diazaindene (9a). Yield 47 mg (26%); mp 156–158 °C; IR ($CHCl_3$): 1730, 1695, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (1H, d, J=11.0 Hz, H-3), 3.69 (3H, s, OC*H*$_3$), 3.80 (1H, d, J=11.0 Hz, H-3), 4.55 (1H, d, J=15.0 Hz, PhC*H*$_2$N), 4.77 (1H, d, J=15.0 Hz, PhC*H*$_2$N), 7.07 (1H, s, H-7), 7.26–7.48 (10H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) 46.8 (t, C-3), 53.3 (q, OCH_3), 54.3 (t, CH_2Ph), 74.6 (s, C-3a), 112.0 (d, C-7), 126.5 (d), 128.3 (d), 129.0 (d), 130.9 (s), 133.8 (s), 134.6 (s), 155.2 (s, C-6), 163.4 (s, O–C=O), 169.0 (s, N–C=O); MS (70 eV) *m/z* 362 ($M^{+\bullet}$, 7.5), 332 (M−NO, 22), 303 (M−$CH_3CO_2^{\bullet}$, 17), 200 (14), 156 (7.5), 91 (100); HRMS (EI) calcd for $C_{21}H_{18}N_2O_4$ (M^+): 362.1266; found: 362.1263.

4.2.1.2. 2-Benzyl-6-(2-methylthiophenyl)-3a-methoxycarbonyl-4-oxa-1-oxo-2,5-diazaindene (9b). Yield 92 mg (45%); mp 153–154 °C; IR ($CHCl_3$) 1728, 1697, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s, SC*H*$_3$), 3.60 (1H, d, J=11.0 Hz, H-3), 3.73 (3H, s, OC*H*$_3$), 3.82 (1H, d, J=11.0 Hz, H-3), 4.55 (1H, d, J=14.6 Hz, PhC*H*$_2$N), 4.75 (1H, d, J=14.6 Hz, PhC*H*$_2$N), 6.83 (1H, s, H-7), 7.25–7.48 (9H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1 (q, SCH_3), 46.6 (t, C-3), 53.1 (q, OCH_3), 54.0 (t, CH_2Ph), 74.4 (s, C-3a), 115.1 (d, C-7), 125.7 (d), 127.7 (d), 128.2 (d), 128.3 (2d), 128.9 (2d), 129.4 (d), 130.7 (d), 131.0 (s), 132.8 (s), 134.8 (s), 138.0 (s), 156.4 (s, C-6), 163.3 (s, O–C=O), 169.1 (s, N–C=O); MS (70 eV) *m/z* 408 ($M^{+\bullet}$, 24), 393 (21), 379 (22), 378 (85), 349 (58), 348 (12), 274 (17), 246 (25), 91 (100), 65 (10); HRMS (EI) calcd for $C_{22}H_{20}N_2O_4S$ (M^+): 408.1144; found: 408.1146.

4.2.1.3. 2-Benzyl-6-(2-ethylthiophenyl)-3a-methoxycarbonyl-4-oxa-1-oxo-2,5-diazaindene (9c). Yield 100 mg (47%); mp 147–149 °C; IR ($CHCl_3$) 1730, 1695, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, SCH_2CH_3), 2.84 (2H, dq, S*CH*$_2$CH$_3$), 3.60 (1H, d, J=10.6 Hz, H-3), 3.72 (3H, s, OC*H*$_3$), 3.81 (1H, d, J=10.6 Hz, H-3), 4.52 (1H, d, J=14.9 Hz, PhC*H*$_2$N), 4.77 (1H, d, J=14.9 Hz, PhC*H*$_2$N), 6.81 (1H, s, H-7), 7.26–7.50 (9H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q, SCH_2CH_3), 28.6 (t, S*CH*$_2$CH$_3$), 46.5 (t, C-3), 53.0 (q, OCH_3), 54.0 (t, CH_2Ph), 74.2 (s, C-3a), 115.2 (d, C-7), 126.5 (d), 128.0 (2d), 128.1 (2d), 128.8 (d), 129.5 (d), 130.3 (d), 130.4 (s), 130.4 (d), 134.4 (s), 134.8 (s), 135.8 (s), 156.7 (s, C-6), 163.2 (s, O–C=O), 169.0 (s, N–C=O); MS (70 eV) *m/z* 422 ($M^{+\bullet}$, 33), 390 (50), 392 (54), 361 (34), 363 (85), 335 (23), 332 (27), 274 (34), 246 (34), 91 (100), 65 (10); HRMS (EI) calcd for $C_{23}H_{22}N_2O_4S$ (M^+): 422.1300; found: 422.1300.

4.2.1.4. 2-Benzyl-6-(2-(2-methyl)propylthiophenyl)-3a-methoxycarbonyl-4-oxa-1-oxo-2,5-diazaindene (9d). Yield 59 mg (26%), two diastereomers; mp 128–132 °C; IR ($CHCl_3$) 1730, 1697, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.33 Hz, CH_2CH_3), 0.94 (3H, t, J=7.32 Hz, CH_2CH_3), 1.18 (3H, d, J=6.23 Hz, $CHCH_3$), 1.20 (3H, d, J=6.59 Hz, $CHCH_3$), 1.40–1.53 (2H, m, CH_3CH_2), 1.53–1.68 (2H, m, CH_3CH_2), 3.04–3.17 (1H, m, CH_3CH), 3.59 (1H, d, J=10.6 Hz, H-3), 3.72 (3H, s, OCH_3), 3.81 (0.5H, d, J=10.6 Hz, H-3), 3.80 (0.5H, d, J=11.0 Hz, H-3), 4.51 (0.5H, d, J=15.0 Hz, $PhCH_2N$), 4.52 (0.5H, d, J=15.0 Hz, $PhCH_2N$), 4.77 (1H, d, J=15.0 Hz, $PhCH_2N$), 6.81 (0.5H, s, H-7), 6.83 (0.5H, s, H-7), 7.20–7.51 (9H, m, 2Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 11.3 (2q, CH_3CH), 20.3 (2q, CH_2CH_3), 29.4, 29.5 (2t, CH_2CH_3), 45.4, 45.8 (2d, CH_3CHCH_2), 46.6 (2t, C-3), 52.98, 53.00 (2q, OCH_3), 54.1 (2t, CH_2Ph), 74.3 (2s, C-3a), 115.57, 115.62 (2d, C-7), 127.1, 127.3 (2d), 128.1 (2d), 128.2 (4d), 128.9 (4d), 129.70, 129.75 (2d), 129.8, 129.9 (2s), 130.41, 130.43 (2d), 133.2, 132.7 (2d), 134.8 (2s), 135.0, 135.1 (2s), 135.8, 136.7 (2s), 156.8 (2s, C-6), 156.9 (2s, C-6), 163.4 (2s, O–C=O), 169.1 (2s, N–C=O); MS (70 eV) *m/z* 450 ($M^{+\bullet}$, 20), 420 (12), 391 (23), 393 (48), 395 (18), 361 (34), 334 (23), 335 (100), 275 (18), 245 (13), 246 (32), 249 (15), 215 (15), 200 (12), 91 (86); HRMS (EI) calcd for $C_{25}H_{26}N_2O_4S$ (M^+): 450.1613; found: 450.1611.

4.2.1.5. Crystal data for 9b. Data collected on a rotating anode (Cu Kα 1.54178 Å). Monoclinic, space group $P2_1/n$, a=8.161(2), b=27.296(4), c=9.950(3) Å, β=113.25(2)°, V=2036.4(8) Å^3, Z=4, ρ_{calcd}=1.332 Mg m^{-3}, θ_{max}=64.76°, temp=293(2) K, no. of measured and independent reflections: 21461/3318, no. of parameters=264, R_1=0.0492, wR_2=0.1422, max residual electron density: 0.214 e/Å^3.

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References and notes

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