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The intramolecular aromatic nucleophilic substitution as a route to tricyclic β-lactams. Synthesis of the novel 4-oxa-7-azabicyclo[4.2.0]octane skeleton

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Abstract—Sodium borohydride-carbonyl reduction of the novel 3-(2-fluoro-5-nitro) phenyl-4-benzoyl-2-azetidinones **3** and **7** gave quantitatively the stereoisomeric carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5**. Treatment of the latter with sodium hydride gave the title compounds **8** and **9**, respectively, with good overall yield. The rationale of the stereochemical relationships outlined in the sequences **3** (or **7**)→**4**→**8** and **3** (or **7**)→**5**→**9** is given according to the conformational and keto-enol equilibria of the reactant(s).

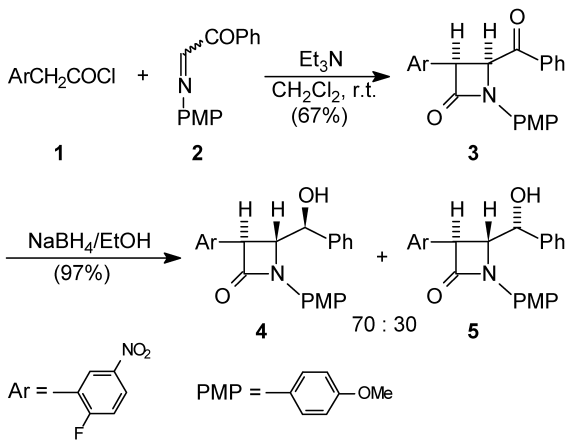
1. Introduction

Since the discovery of penicillin in 1928, 2-azetidinone-based heterocycles have been one of the main class of drugs used for the treatment of bacterial infections.[1] Hence, a number of efforts have been concerned to the synthesis of new β-lactam antibiotics with either different and/or broader antibacterial activity.[2] Lately, the discovery that β-lactameses caused resistance to some penicillins and cephalosporins sped up the search for new drugs which should display enhanced stability towards the β-lactamases.[3] Among those drugs, tricyclic β-lactams appeared as very promising candidates.[4] Following our recent work in the synthesis of novel tricyclic β-lactams,[5] we present here a short and convenient route to the hitherto unknown 4-oxa-7-azabicyclo[4.2.0]octane skeleton which is based upon an intramolecular aromatic nucleophilic substitution as the key step.

2. Results and discussion

2.1. Carbonyl reduction of 4-benzoyl-2-azetidinones 3 and 7

The 3,4-*cis*-4-benzoyl-2-azetidinone **3**, which was devised as the suitable starting material, was synthesised by base treatment of (2-fluoro-5-nitro)phenylacetyl chloride **1**[6] in the presence of imine **2**,[7] thus following the standard Staudinger [2+2] cycloaddition protocol (Scheme 1). Carbonyl reduction of **3** was accomplished with sodium borohydride giving quantitatively the stereoisomeric 3,4-*trans* carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5**. The structures were assigned unambiguously by analytical and spectral data. In particular, as far as ^{1}H NMR is concerned, the arrangement of the two hydrogens in the 4- and the 5-positions can be argued from their vicinal scalar coupling constants, since the J_{trans}=2.4 Hz for (4*R**,5*S**)-**4** and the J_{cis}=5.9 Hz for (4*R**,5*R**)-**5** are found in some literature precedents.[8] Furthermore, the hydrogens in the 3- and 4-positions of the azetidinone ring show mutual scalar couplings of 2.7 and 2.8 Hz, which are in full agreement with the depicted 3,4-*trans* stereochemistry of both



Scheme 1.

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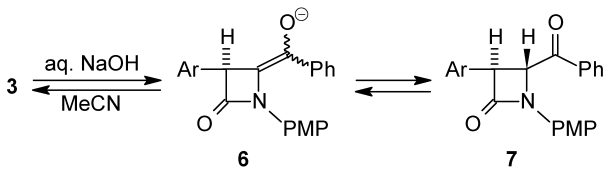
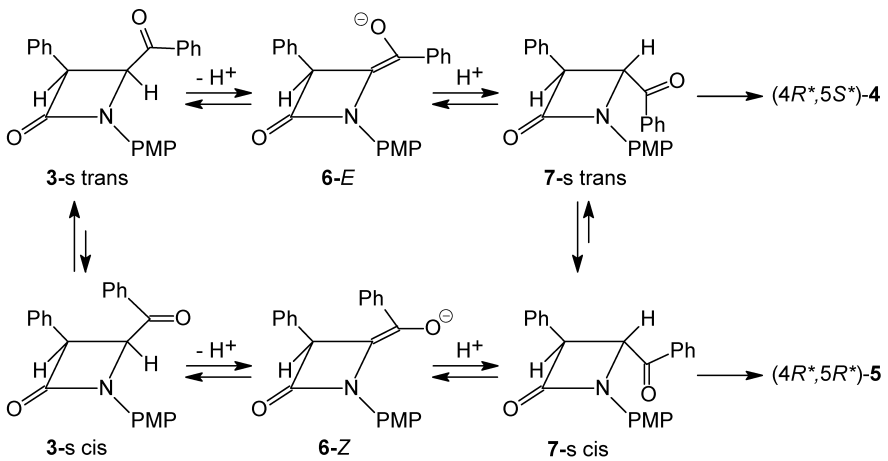


Scheme 2.

Table 1. $NaBH_4$ Carbonyl reduction of 2-azetidinones **3** and **7**

Entry	Time (min)	Products and yields (%)		Yield ratio
		(4*R**,5*S**)-**4**	(4*R**,5*R**)-**5**	**4**:**5**
3	80	68	29	70:30
7	10	29	68	30:70

upon the **4**:**5** ratio when reducing **3** or **7**, let us consider the conformational equilibria outlined in the Scheme 3. When starting from **7**, the left-handed part of Scheme 3 can be ignored since only the two conformations **7**-s *cis* and **7**-s *trans* should be taken into account. It is reasonable that, due to the Ph-PMP steric crowding, the **7**-s *cis* conformation should be favoured with respect to the **7**-s *trans* one, thus providing a qualitative rationale for the experimental 30:70 ratio for carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5**, respectively. On the other hand, with **3** as the starting reagent, the two conformations **3**-s *trans* and **3**-s *cis* needs to be considered first. Due to the Ar-Ph destabilizing interactions, the former conformation should be favoured thus giving preferably the **7**-s *trans* one via the *E* enolate **6**-*E*. The 70:30 ratio in favour of the carbinol (4*R**,5*S**)-**4** can be accounted for provided that carbonyl reduction is not slow towards the conformational interchange between **7**-s *trans* and **7**-s *cis*, as

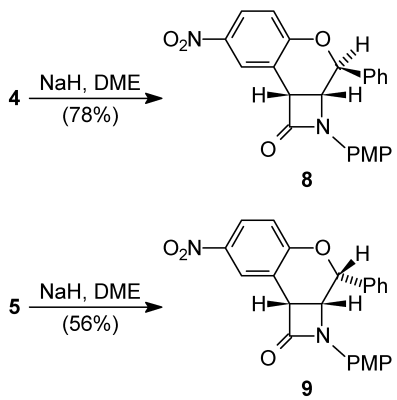


Scheme 3.

(4*R**,5*S**)-**4** and (4*R**,5*R**)-**5**.[7] It was also noted that 3,4-*cis* **3** isomerizes to 3,4-*trans* **7** upon treatment with sodium hydroxide in water-acetonitrile medium (Scheme 2). In these conditions, after 24 h the ^1H NMR analysis of the reaction crude showed a mixture of **3** and **7** in the ratio 33:67. For the sake of comparison, pure **7** was submitted to carbonyl reduction with $NaBH_4$ affording a mixture of (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5** in the ratio 30:70. Reaction times, product yield and ratios for the step **3**→**4**+**5** and **7**→**4**+**5** are summarised in Table 1. Two main statements arise from the above experimental findings and deserve some comments: (i) the 3,4-*cis* stereochemistry of starting **3** is reversed in the reduction step giving only the 3,4-*trans* carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5**, and (ii) by reduction of **7** rather than **3**, the **4**:**5** ratio is just reversed. Due to the basicity of the $NaBH_4$/EtOH medium, isomerisation from 3,4-*cis* **3** to 3,4-*trans* **7** can occur in the reduction step via abstraction of the proton in the 4-position of the 2-azetidinone ring. This picture is consistent with that reported recently for the isomerization of 3,4-*cis*-3-substituted-4-formyl-2-azetidinones.[7,9] After equilibration, 3,4-*trans* **7** undergoes fast carbonyl reduction to carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5** until **3** has completely disappeared from the reaction mixture. This is further substantiated from the reaction times reported in Table 1; carbonyl reduction of **7** is quite fast, while **3** requires much more time in order to equilibrate to **7**. To gain some insight it can be perceived from the fast carbonyl reduction of pure **7**.

2.2. Ring closure of carbinols (4*R**,5*S**)-4 and (4*R**,5*R**)-5

Intramolecular aromatic nucleophilic substitution onto stereoisomeric 3,4-*trans* carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5** was accomplished by treating the latter compounds with sodium hydride in dry dimethoxyethane at room temperature (Scheme 4). The resulting 4-oxa-7-azabicyclo[4.2.0]octanes **8** and **9** were obtained as single



Scheme 4.

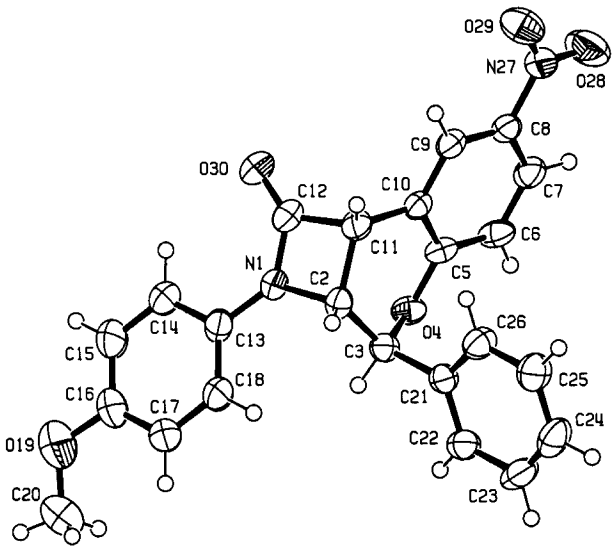


Figure 1. ORTEPIII[12] plot of **8** with the crystallographic numbering scheme. Ellipsoids at 50% probability level. H atoms not to scale.

stereoisomers with good yield. Surprisingly, we found that the hydrogens in the 3- and 4-positions of the 2-azetidinone ring of both **8** and **9** show vicinal coupling constants between 5.8 and 6.1 Hz, which speaks in favour of the depicted 3,4-*cis* stereochemistry.[10] The X-ray diffractometric analysis[11] of **8**[12] fully supports this finding (Fig. 1). Therefore, the ring closure step **4**→**8** and **5**→**9** involves the *trans*→*cis* isomerization of the 2-azetidinone ring. As it can be inferred from Scheme 5, initial deprotonation of the hydroxyl group of (4*R**,5*S**)-**4** should be followed by intramolecular hydrogen abstraction to give the intermediate **11**. Subsequent intramolecular hydrogen 1,4-shift should generate the 3,4-*cis*-2-azetidino-5-alkoxide intermediate **12** in a reversible way, while irreversible fluorine displacement from **12** just gives **8**. As an alternative mechanistic pathway, intermediate **11** could be generated directly from (4*R**,5*S**)-**4** due to the marked acidity of the hydrogen in the 3-position of the 2-azetidinone ring.[13] Irrespective from the above mechanistic hypothesis, intermediate 3,4-*cis* **12** is the only reasonable candidate for the ring closure to **8**, this possibility being precluded to 3,4-*trans* **10** for steric reasons. Obviously, the same considerations also applies to the ring closure step **5**→**9**.

3. Conclusions

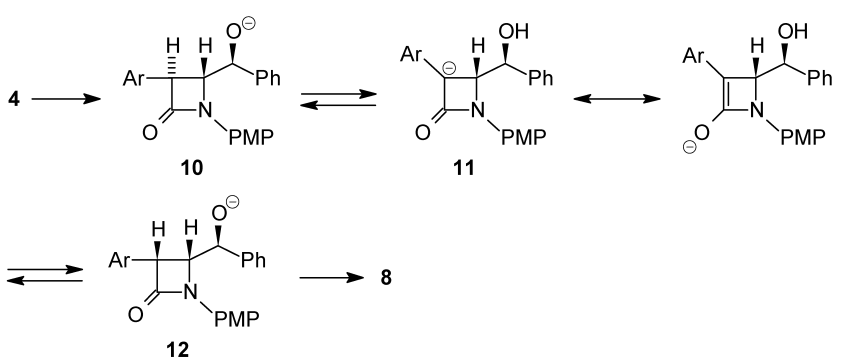
The formation of carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5** from the carbonyl reduction of 4-benzoyl-2-azetidinones **3** and **7** is the result of a complex interplay of conformational and keto-enol equilibria between the reactant(s), whose rationalisation provided a qualitative insight of the **4**:**5** ratio. Furthermore, owing to the good overall yield for both the sequences **1**→**8** and **1**→**9**, our three-steps approach constitutes a valuable tool for the multi-gram synthesis of novel 4-oxa-7-azabicyclo[4.2.0]octanes of potential pharmaceutical interest.

4. Experimental

4.1. General

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz.

4.1.1. [1-(4-Methoxyphenyl)-3(S*)-(2-fluoro-5-nitrophenyl)-4(S*)-benzoyl]-2-azetidinone 3. A solution of 2-fluoro-5-nitrophenylacetyl chloride **1** (3.60 g, 16.5 mmol) in dry dichloromethane (40 mL) was added dropwise to a solution of *N*-(4-methoxyphenyl)-glyoxalimine **2** (0.96 g, 4.0 mmol) and Et_3N (3.9 mL, 28.0 mmol) in dry dicholromethane (30 mL) at room temperature. The reaction was monitored by TLC with light petroleum/ethyl acetate 65:35 as the eluent. After 4 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (2×25 mL) and the organic layer was washed with water to pH 7. The solvent was evaporated at reduced pressure, and the residue was chromatographed on a silica gel column with light petroleum/ethyl acetate 65:35 affording **3** (1.14 g, 68%). Pale orange solid; mp 154–155°C (from ethanol); IR (nujol) 1750, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 5.32 (d, *J*=6.4 Hz, 1H), 5.93 (d, *J*=6.4 Hz, 1H), 6.91–8.23 (m, 12H); ^{13}C ($CDCl_3$) δ 51.1 (CH), 55.5 (CH_3), 59.9 (CH), 114.4 (CH), 115.9 (CH,



Scheme 5.

J_{CF}=22.6 Hz), 116.0 (CH), 118.7 (CH), 120.6 (Cq, J_{CF}=15.1 Hz), 126.0 (CH, J_{CF}=15.1 Hz), 126.6 (CH, J_{CF}=7.5 Hz), 128.0 (CH), 128.6 (CH), 128.8 (CH), 130.6 (Cq), 144.1 (Cq), 156.8 (Cq), 160.9 (Cq), 163.9 (Cq, J_{CF}=256.6 Hz), 192.5 (Cq); MS *m/z* 420 (M^+). Anal. calcd for $C_{23}H_{17}FN_2O_5$: C, 65.71; H, 4.08; N, 6.66. Found: C, 65.66; H, 4.04; N, 6.71.

4.1.2. Sodium hydroxide-promoted isomerization of 3 to 7. A solution of NaOH (0.11 g, 2.8 mmol) in water (2.0 mL) was added to a solution of **3** (0.58 g, 1.4 mmol) in acetonitrile (16 mL) at room temperature and stirred for 24 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with dichloromethane (3×10 mL) and washed with water to pH 7. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column with light petroleum/ethyl acetate 65:35.

First fractions gave **7** (0.36 g, 62%). Pale orange solid; mp 115–116°C (from ethanol); IR (nujol) 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 4.60 (d, *J*=3.0 Hz, 1H), 5.50 (d, *J*=3.0 Hz, 1H), 6.91–8.23 (m, 12H); ^{13}C ($CDCl_3$) δ 53.9 (CH), 55.5 (CH_3), 60.7 (CH), 114.5 (CH), 117.2 (CH, J_{CF}=24.2 Hz), 118.7 (CH), 122.9 (Cq, J_{CF}=16.8 Hz), 125.8 (CH, J_{CF}=5.4 Hz), 126.3 (CH, J_{CF}=10.3 Hz), 128.2 (CH), 129.3 (CH), 130.5 (Cq), 134.1 (CH), 134.8 (CH), 144.7 (Cq), 156.9 (Cq), 160.8 (Cq), 164.4 (Cq, J_{CF}=259.2 Hz), 193.2 (Cq); MS *m/z* 420 (M^+). Anal. calcd for $C_{23}H_{17}FN_2O_5$: C, 65.71; H, 4.08; N, 6.66. Found: C, 65.74; H, 4.11; N, 6.71.

Further elution gave unreacted **3** (0.19 g, 33%)

4.1.3. Carbinols (4*R,5*S**)-4 and (4*R**,5*R**)-5. General procedure.** $NaBH_4$ (90 mg, 2.3 mmol) was added to a suspension of **3** or **7** (0.94 g, 2.2 mmol) in ethanol (25 mL) at room temperature. After 80 min (when starting from **3**) or 10 min (when starting from **7**) the reaction mixture was diluted with water (25 mL) and then concentrated at reduced pressure to about half volume. The resulting mixture was extracted with dichloromethane (3×25 mL), the organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed on a silica gel column with light petroleum/*t*-BuOMe 1:1. (4*R**,5*S**)-**4** was eluted first, followed by (4*R**,5*R**)-**5**. Isolated yields of the isomeric carbinols (4*R**,5*S**)-**4** and (4*R**,5*R**)-**5** are summarised in the Table 1.

(4*R**,5*S**)-**4**. White solid; mp 67–68°C (from ethanol); IR (nujol) 3400, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (br d, *J*=2.9 Hz, 1H), 3.83 (s, 3H), 4.32 (dd, *J*=2.7, 2.6 Hz, 1H), 4.73 (d, *J*=2.6 Hz, 1H), 5.4 (dd, *J*=2.7, 2.9 Hz, 1H), 6.95–8.23 (m, 12H); ^{13}C ($CDCl_3$) δ 48.6 (CH), 55.5 (CH_3), 64.3 (CH), 70.0 (CH), 114.6 (CH), 116.6 (CH, J_{CF}=30.2 Hz), 119.4 (CH), 123.9 (Cq, J_{CF}=15.1 Hz), 125.2 (CH, J_{CF}=15.1 Hz), 125.8 (CH, J_{CF}=7.5 Hz), 128.5 (CH), 128.6 (CH), 128.7 (CH), 130.1 (Cq), 138.6 (Cq), 144.2 (Cq), 156.8 (Cq), 162.5 (Cq), 164.0 (Cq, J_{CF}=218.9 Hz); MS *m/z* 422 (M^+). Anal. calcd for $C_{23}H_{19}FN_2O_5$: C, 65.40; H, 4.53; N, 6.63. Found: C, 65.34; H, 4.50; N, 6.58.

(4*R**,5*R**)-**5**. White solid; mp 74–75°C (from ethanol); IR (nujol) 3390, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (br s, 1H), 3.80 (s, 3H), 4.22 (d, *J*=2.8 Hz, 1H), 4.41 (dd, *J*=2.8, 5.9 Hz, 1H), 5.19 (d, *J*=5.9 Hz, 1H), 6.90–8.15 (m, 12H); ^{13}C ($CDCl_3$) δ 51.0 (CH), 55.5 (CH_3), 64.2 (CH), 75.1 (CH), 114.2 (CH), 116.6 (CH, J_{CF}=30.2 Hz), 120.1 (CH), 123.7 (Cq, J_{CF}=22.3 Hz), 125.3 (CH, J_{CF}=15.1 Hz), 125.7 (Cq, J_{CF}=3.8 Hz), 126.3 (CH), 128.8 (CH), 128.9 (CH, J_{CF}=7.5 Hz), 130.5 (Cq), 139.1 (Cq), 144.2 (Cq), 156.7 (Cq), 162.5 (Cq), 164.4 (Cq, J_{CF}=226.4 Hz); MS *m/z* 422 (M^+). Anal. calcd for $C_{23}H_{19}FN_2O_5$: C, 65.40; H, 4.53; N, 6.63. Found: C, 65.43; H, 4.56; N, 6.67.

4.1.4. 4-Oxa-7-azabicyclo[4.2.0]octanes 8 and 9. A solution of **4** or **5** (98 mg, 0.23 mmol) in dry dimethoxyethane (3.0 mL) was slowly added to a suspension of NaH (12 mg, 0.5 mmol) in dry dimethoxyethane (1.5 mL) under nitrogen atmosphere. After 15 min (when starting from **4**) or 45 min (when starting from **5**) the mixture was quenched with water and extracted with dichloromethane (3×5 mL). The organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was crystallised from isopropyl ether giving analytically pure **8** or **9**.

Compound **8** (73 mg, 78%). White solid; mp 205–206°C (from ethanol); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.22 (d, *J*=2.8 Hz, 1H), 4.41 (dd, *J*=2.8, 5.9 Hz, 1H), 5.19 (d, *J*=5.9 Hz, 1H), 6.90–8.15 (m, 12H); ^{13}C ($CDCl_3$) δ 48.4 (CH), 55.4 (CH), 55.5 (CH_3), 75.4 (CH), 114.7 (CH), 119.2 (CH), 120.1, 124.9 (CH), 127.4 (CH), 129.0 (CH), 129.3 (CH), 136.0 (Cq), 142.8 (Cq), 156.9 (Cq), 157.7 (Cq), 160.8 (Cq); MS *m/z* 402 (M^+). Anal. calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.61; H, 4.54; N, 7.00.

Compound **9** (52 mg, 56%). White solid; mp 237–240°C (from ethanol); IR (nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.22 (d, *J*=2.8 Hz, 1H), 4.41 (dd, *J*=2.8, 5.9 Hz, 1H), 5.19 (d, *J*=5.9 Hz, 1H), 6.90–8.15 (m, 12H); ^{13}C ($CDCl_3$) δ 50.1 (CH), 55.3 (CH_3), 59.0 (CH), 78.9 (CH), 113.6 (CH), 118.8 (CH), 119.6 (CH), 120.4 (Cq), 124.6 (CH), 125.3 (CH), 126.1 (CH), 128.5 (CH), 128.6 (CH), 130.1 (Cq), 135.7 (Cq), 143.2 (Cq), 156.1 (Cq), 161.0 (Cq), 161.8 (Cq); MS *m/z* 402 (M^+). Anal. calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.68; H, 4.54; N, 6.91.

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