A One-Pot, Ugi Four-Component Synthesis of 2(3*H*)-Oxazolone 4-Carboxamides

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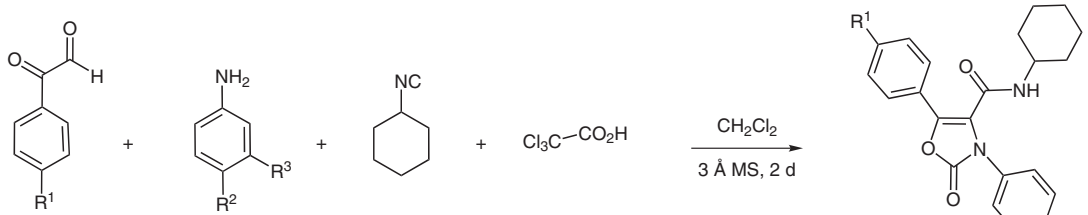
Abstract: Ugi reaction between arylglyoxals, anilines, cyclohexyl isocyanide and trichloroacetic acid in dichloromethane, in the presence of molecular sieves, afforded 2(3*H*)-oxazolone 4-carboxamides in good yields by a one-pot process that involved an in situ spontaneous cyclization of the Ugi product through an intermediate ketone enolate and the chloroacetate carbonyl group. The synthesis is based on the ability of the trichloroacetyl group to function as a masked carbonic acid surrogate.

Key words: isocyanide, arylglyoxal, trichloroacetic acid, oxazolone

The aryloxazolone moiety is found in the structure of some nonsteroidal anti-inflammatory drugs that are potent and selective COX-2 inhibitors,[1] but oxazolones with a carboxyl group at the 4-position are relatively uncommon, which is somewhat surprising considering that the oxazolone moiety incorporates dense functionality and great utility in synthesis.[2] Very few syntheses of 2(3*H*)-oxazolone-4-carboxylic acid derivatives have been reported.[3] The rather complex and non-general reported methodologies could have hindered the availability of this nucleus for practical applications such as the well-known ones developed for the dihydro compounds, namely 2-oxo-4-oxazolidinecarboxylic acid derivatives.[4] We have recently shown that the sequences of classical Ugi or Passerini isocyanide multicomponent reactions, followed by post-condensation transformations, constitute extremely powerful synthetic tools for the preparation of structurally diverse complex molecules, such as heterocyclic compounds with elaborate substitution patterns, constrained peptides, peptide mimetics, and pseudopeptides.[5] As a new contribution of this methodology, we report in this paper a new one-pot synthesis of 3,5-diaryl-2(3*H*)-oxazolone 4-carboxamides by the Ugi reaction between arylglyoxals **1**, anilines **2**, cyclohexyl isocyanide (**3**), and trichloroacetic acid (**4**), followed by spontaneous in situ cyclization reaction of the presumably initially formed Ugi products (Scheme 1).

Arylglyoxals **1** were prepared in good yields by the general method of Riley and Gray,[6] following the modification by Arnold and Fuson,[7] to prevent the formation of the glyoxal hydrate. Thus, a mixture of freshly distilled arylglyoxal **1a–e** (1 equiv) and aniline **2a–e** (1.2 equiv) in dichloromethane was stirred at room temperature in the presence of 3 Å molecular sieves for ten minutes. Then cyclohexyl isocyanide[8] (**3**; 1 equiv) and anhydrous trichloroacetic acid (**4**; 1 equiv) were added and the mixture was stirred at room temperature for two days. Filtration of the molecular sieves and evaporation of the solvent afforded a sticky residue that was stirred with diethyl ether until solid *N*-cyclohexyl 3,5-diaryl-2(3*H*)-oxazolone 4-carboxamides **5a–m** were obtained in good yields (61–89%; Table 1).[9]



1a: R^1 = H
1b: R^1 = Me
1c: R^1 = Cl
1d: R^1 = OMe
1e: R^1 = F

2a: R^2 = H; R^3 = H
2b: R^2 = Me; R^3 = H
2c: R^2 = OMe; R^3 = H
2d: R^2 = Cl; R^3 = H
2e: R^2 = H; R^3 = Cl

Scheme 1

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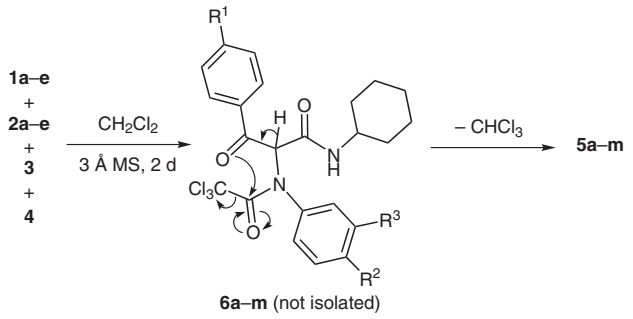
Table 1 Synthesis of Oxazolones **5a–m**

5	R^1	R^2	R^3	Yield (%) 3 Å MS	Yield (%) amine (2 equiv)
5a	H	H	H	85	64
5b	H	Me	H	89	58
5c	H	OMe	H	72	56
5d	Me	H	H	88	61
5e	Me	Me	H	83	56
5f	Me	OMe	H	71	55
5g	Me	Cl	H	69	51
5h	Cl	H	H	88	65
5i	Cl	Me	H	81	61
5j	Cl	OMe	H	62	52
5k	OMe	OMe	H	61	49
5l	OMe	H	Cl	62	53
5m	F	H	H	65	51

The recrystallized products were easily characterized by the usual spectroscopic and analytical techniques. Single crystal X-ray diffraction of one of the samples, **5b**, confirmed the oxazolone structure.[10]

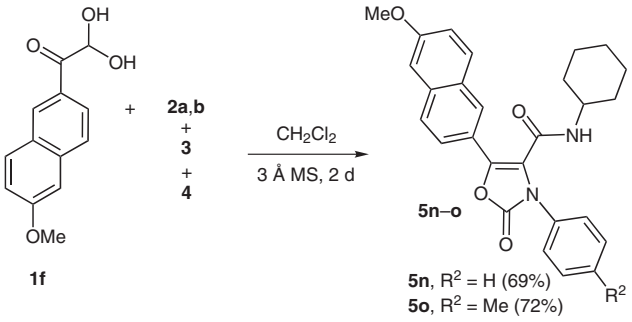
We supposed that the expected Ugi products **6a–m** were initially formed under the reaction conditions, subsequently undergoing spontaneous cyclization by attack of the ketone enolate onto the chloroacetate carbonyl group, consequently eliminating chloroform and affording irreversibly the oxazolones **5a–m** (Scheme 2). The high solubility of the products in dichloromethane prevented the usual precipitation of the Ugi products, thus allowing a smooth cyclization to the products. This reaction is an example of the known ability of the trichloroacetyl group to function as a masked carbonic acid surrogate.[5b]



Scheme 2

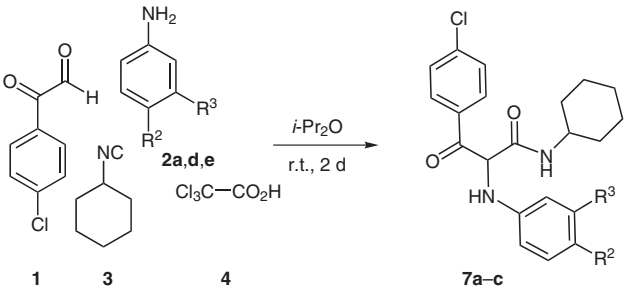
To extend the scope of the reaction we then performed the reaction by using two commercial arylglyoxal hydrates, **1e**·H_2O and **1f**·H_2O. First, hydrate **1e**·H_2O was subjected to the above-described reaction conditions, from which oxazolone **5m** was obtained in comparable yield (63%).

We then applied the same methodology to **1f**·H_2O and **2a**,**b**, **3** and **4**, from which oxazolones **5n–o** were obtained in 69–72% yields (Scheme 3). Therefore the presence of an additional equivalent of water had no influence on the reaction yields if sufficient 3 Å molecular sieves were present to absorb water produced during the Ugi condensation.



Scheme 3

The presence of water has been reported to accelerate the Ugi reaction[11] but in our case, in the absence of 3 Å molecular sieves, a mixture of **1a** (1 equiv), **2b** (1 equiv), **3** (1 equiv) and **4** (1 equiv) in dichloromethane, stirred for two days at room temperature, afforded **5b** in 31% yield. MS of the reaction residue showed distinct peaks of cyclohexylformamide, tolyl trichloroacetamide and deacylated Ugi product. In the same way, reaction of **1c** (1 equiv), **2a**,**d**,**e** (1 equiv), **3** (1 equiv) and **4** (1 equiv) in isopropyl ether, stirred for two days at room temperature, produced the deacylated Ugi products **7a–c** (35–48%) as the main products, showing only traces of the oxazolones by MS of the reaction residue (Scheme 4, Table 2).[12]



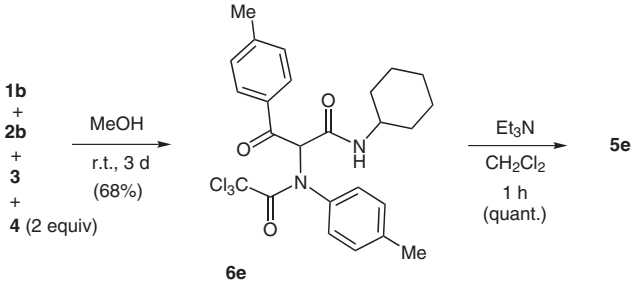
Scheme 4

Table 2 Synthesis of Deacylated Products **7a–c**

7	R^2	R^3	Yield (%)
7a	H	H	35
7b	Cl	H	42
7c	H	Cl	48

In all these reactions water may act as the acid component in the presence of the strongly acidic trichloroacetic acid, but the action of water can be minimized in alkaline envi-

ronment. Thus, in the presence of two equivalents of starting aniline, a mixture of arylglyoxals **1a–e** (1 equiv), anilines **2a–e** (2 equiv), cyclohexyl isocyanide (**3**; 1 equiv) and trichloroacetic acid (**4**; 1 equiv) in dichloromethane, stirred for two days, afforded the same oxazolones **5a–m**, although in lower yields (Table 1). On the other hand, in the presence of two equivalents of trichloroacetic acid, a mixture of reagents **1b** (1 equiv), **2b** (1 equiv) and **3** (1 equiv) in methanol, stirred at room temperature for three days, afforded exclusively the Ugi product **6e**, probably due to the fact that its solubility was sufficiently low to precipitate in the reaction environment as it was formed (Scheme 5).[13]



Scheme 5

The obtained Ugi product **6e** was a stable solid,[14] but when treated with triethylamine (2 equiv) in dichloromethane at room temperature for one hour, it afforded quantitatively the corresponding oxazolone **5e** (Scheme 5). Under the same conditions, a mixture of **1b** (1 equiv), **2a** (1 equiv), **3** (1 equiv) and **4** (2 equiv) afforded the corresponding oxazolone **5a** in 62% yield, indicating that the cyclization was also catalyzed by acid. Because of the uncertainty of the results, this method was not further studied. Some of the reported oxazolones were remarkably fluorescent in acetonitrile solution. As a representative example, the colorless (λ_{max} = 287 nm, $\varepsilon = 2 \times 10^4$ $Lmol^{-1}cm^{-1}$) oxazolone **5f** (10^{-4} M in MeCN) fluoresced at 432 nm and 462 nm (λ_{ex} = 298 nm).

In summary, we have described the synthesis of new *N*-cyclohexyl 3,5-diaryl-2(3*H*)-oxazolone 4-carboxamides by means of a very simple one-pot Ugi four-component condensation followed by spontaneous cyclization to the final products. The reaction employs all commercial or easily available starting materials, is performed under very simple experimental conditions and does not require chromatographic workup, but only recrystallization of the products, therefore being appropriate for combinatorial schemes.

Acknowledgment

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(9) **Synthesis of 2 (3*H*)-Oxazolone 4-Carboxamides 5a–m**: A mixture of freshly distilled arylglyoxal (1 mmol), the corresponding arylamine (1.2 mmol) and activated 3 Å MS (1 g) in CH_2Cl_2 (10 mL) was stirred at r.t. for 10 min. Then cyclohexyl isocyanide (110 mg, 1 mmol) and anhyd trichloroacetic acid (162 mg, 1 mmol) were consecutively added and the mixture was stirred at r.t. for 2 d, then filtered and the solvent was evaporated under reduced pressure. The sticky residue was stirred with Et_2O (10 mL) until a solid separated. The solid was filtered and recrystallized from the appropriate solvent.
***N*-Cyclohexyl-2-oxo-3,5-diphenyl-2,3-dihydrooxazole-4-carboxamide (5a)**: colorless crystals (308 mg, 85%); mp 230–231 °C (*i*-Pr_2O–*i*-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.93 (m, 2 H), 0.98–1.10 (m, 1 H), 1.18–1.29 (m, 2 H), 1.50–1.61 (m, 3 H), 1.64–1.74 (m, 2 H), 3.73–3.81 (m, 1 H), 5.45 (d, *J* = 8.0 Hz, 1 H), 7.38–7.49 (m, 8 H), 7.76–7.79 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_2), 25.1 (CH_2), 32.1 (CH_2), 48.6 (CH), 119.1 (C_q), 125.5 (CH_{Ar}),

126.1 (C_q), 126.3 (CH_{Ar}), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 129.4 (CH_{Ar}), 129.6 (CH_{Ar}), 133.7 (C_q), 139.1 (C_q), 152.5 (C_q), 157.1 (C_q). IR (KBr): 3254, 1770, 1630 cm^{-1}. MS (EI): *m*/*z* (%) = 362 (69) [M^+], 279 (100). HRMS (EI): *m*/*z* calcd for $C_{22}H_{22}N_2O_3$: 362.1630; found: 362.1632. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.97; H, 6.16; N, 7.67.

3-(4-Chlorophenyl)-*N*-cyclohexyl-2-oxo-5-*p*-tolyl-2,3-dihydrooxazole-4-carboxamide (5g): colorless crystals (284 mg, 69%); mp 232–233 °C (*i*-Pr_2O–*i*-PrOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.10 (m, 3 H), 1.20–1.34 (m, 2 H), 1.55–1.63 (m, 3 H), 1.75–1.79 (m, 2 H), 2.39 (s, 3 H), 3.75–3.84 (m, 1 H), 5.61 (d, *J* = 8.2 Hz, 1 H), 7.22–7.25 (m, 2 H), 7.32–7.35 (m, 2 H), 7.40–7.44 (m, 2 H), 7.57–7.59 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (Me), 24.8 (CH_2), 25.4 (CH_2), 32.6 (CH_2), 49.0 (CH), 118.4 (C_q), 123.3 (C_q), 126.9 (CH_{Ar}), 127.1 (CH_{Ar}), 129.7 (CH_{Ar}), 129.8 (CH_{Ar}), 132.8 (C_q), 134.4 (C_q), 140.0 (C_q), 140.7 (C_q), 152.7 (C_q), 157.2 (C_q). IR (KBr): 3282, 1774, 1663, 1635, 1495 cm^{-1}. MS (EI): *m*/*z* (%) = 412 (16) [M^+ + 2], 410 (57) [M^+], 327 (84), 119 (100). HRMS (EI): *m*/*z* calcd for $C_{23}H_{23}ClN_2O_3$: 410.1397; found: 410.1382. Anal. Calcd for $C_{23}H_{23}ClN_2O_3$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.28; H, 5.67; N, 6.77.

5-(4-Chlorophenyl)-*N*-cyclohexyl-2-oxo-3-phenyl-2,3-dihydrooxazole-4-carboxamide (5h): colorless crystals (349 mg, 88%); mp 224–226 °C (dec., *i*-Pr_2O–*i*-PrOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.88 (m, 2 H), 0.98–1.08 (m, 1 H), 1.18–1.30 (m, 2 H), 1.51–1.68 (m, 5 H), 3.71–3.79 (m, 1 H), 5.37 (d, *J* = 8.0 Hz, 1 H), 7.38–7.49 (m, 7 H), 7.75–7.77 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2), 25.4 (CH_2), 32.5 (CH_2), 48.9 (CH), 119.5 (C_q), 125.0 (C_q), 125.9 (CH_{Ar}), 128.0 (CH_{Ar}), 129.0 (CH_{Ar}), 129.2 (CH_{Ar}), 129.9 (CH_{Ar}), 131.7 (C_q), 133.9 (C_q), 135.9 (C_q), 139.2 (C_q), 152.5 (C_q), 157.1 (C_q). IR (KBr): 3305, 1789, 1658, 1632 cm^{-1}. MS (EI): *m*/*z* (%) = 398 (24) [M^+ + 2], 396 (100) [M^+], 313 (59), 315 (19). HRMS (EI): *m*/*z* calcd for $C_{22}H_{21}ClN_2O_3$: 396.1241; found: 396.1233. Anal. Calcd for $C_{22}H_{21}ClN_2O_3$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.53; H, 5.29; N, 7.01.

3-(3-Chlorophenyl)-*N*-cyclohexyl-5-(4-methoxyphenyl)-2-oxo-2,3-dihydrooxazole-4-carboxamide (5l): colorless crystals (265 mg, 62%); mp 240–241 °C (dec., *i*-Pr_2O–*i*-PrOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.30 (m, 5 H), 1.53–1.61 (m, 3 H), 1.75–1.79 (m, 2 H), 3.77–3.83 (m, 1 H), 3.85 (s, 3 H), 5.49 (d, *J* = 8.4 Hz, 1 H), 6.94–6.96 (m, 2 H), 7.32–7.41 (m, 4 H), 7.67–7.69 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (CH_2), 25.4 (CH_2), 32.6 (CH_2), 48.9 (CH), 55.6 (Me), 114.5 (CH_{Ar}), 117.5 (C_q), 118.6 (C_q), 123.9 (CH_{Ar}), 126.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 130.5 (CH_{Ar}), 135.2 (C_q), 152.5 (C_q), 157.2 (C_q), 161.2 (C_q). IR (KBr): 3418, 3247, 1773, 1661, 1632, 1607 cm^{-1}. MS (EI): *m*/*z* (%) = 428 (13) [M^+ + 2], 426 (47) [M^+], 135 (100). HRMS (EI): *m*/*z* calcd for $C_{23}H_{23}ClN_2O_4$: 426.1346; found: 426.1329. Anal. Calcd for $C_{23}H_{23}ClN_2O_4$: C, 64.71; H, 5.43; N, 6.56. Found: C, 64.66; H, 5.38; N, 6.51.

(10) **Crystal Data for Compound 5b**: $C_{23}H_{24}N_2O_3$, MW = 376.44, orthorhombic, $P2_12_12_1$, *a* = 9.038(5) Å, *b* = 10.536 (5) Å, *c* = 21.916(11) Å, α = 90°, β = 90°, γ = 90°; *V* = 2087.1(18) $Å^3$, *Z* = 4, D_{calc} = 1.198 gcm^{-1}, μ(Mo–K_a) = 0.080 mm^{-1}. Colorless prism (0.30 × 0.20 × 0.10 mm^3), 19410 measured reflections, 3658 independent (R_{int} = 0.0968), 2247 observed [I > 2σ(I)]. *R*1 = 0.1434, *wR*2 = 0.2444 (all data). CCDC 664815 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk.

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(12) **Synthesis of Deacylated Ugi Products 7a–c; General Procedure**: A mixture of *p*-chlorophenylglyoxal (169 mg, 1 mmol) and the corresponding arylamine (1 mmol) in *i*-Pr_2O (10 mL) was stirred at r.t. for 10 min. Then cyclohexyl isocyanide (110 mg, 1 mmol) and anhyd trichloroacetic acid (163 mg, 1 mmol) were consecutively added and the mixture was stirred at r.t. for 2 d. The solid residue was filtered and then recrystallized from the *i*-Pr_2O–*i*-PrOH mixture.

3-(4-Chlorophenyl)-*N*-cyclohexyl-3-oxo-2-(phenylamino)propionamide (7a): colorless crystals (130 mg, 35%); mp 164–165 °C (*i*-Pr_2O–*i*-PrOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89–1.13 (m, 3 H), 1.20–1.32 (m, 2 H), 1.48–1.83 (m, 5 H), 3.57–3.68 (m, 1 H), 5.31 (d, *J* = 3.0 Hz, 1 H), 5.43 (d, *J* = 3.0 Hz, 1 H), 6.68–6.71 (m, 2 H), 6.80–6.85 (m, 2 H), 7.21–7.24 (m, 2 H), 7.44–7.46 (m, 2 H), 8.21–8.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH_2), 24.6 (CH_2), 25.2 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 48.6 (CH), 66.6 (CH), 113.8 (CH_{Ar}), 119.4 (CH_{Ar}), 128.7 (CH_{Ar}), 129.5 (CH_{Ar}), 131.8 (CH_{Ar}), 132.3 (C_q), 140.9 (C_q), 145.5 (C_q), 165.8 (C_q), 193.0 (C_q). IR (KBr): 3390, 3298, 1695, 1654 cm^{-1}. MS (EI): *m*/*z* (%) = 372 (7) [M^+ + 2], 370 (24) [M^+], 245 (100), 231 (99), 104 (69). HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}ClN_2O_2$: 370.1448; found: 370.1443. Anal. Calcd for $C_{21}H_{23}ClN_2O_2$: C, 68.01; H, 6.25; N, 7.55. Found: C, 67.94; H, 5.95; N, 7.48.

(13) For a complete discussion about the effect of reagents and solvents in the Ugi reaction, see: Marcaccini, S.; Torroba, T. *Nature Prot.* **2007**, *2*, 632.

(14) **Synthesis of *N*-Cyclohexyl-3-oxo-3-*p*-tolyl-2-(2,2,2-trichloro-*N*-*p*-tolylacetamido)propionamide (6e)**: A mixture of *p*-tolylglyoxal (148 mg, 1 mmol) and *p*-toluidine (107 mg, 1 mmol) in MeOH (10 mL) was stirred for 10 min, and then cyclohexyl isocyanide (110 mg, 1 mmol) and anhyd trichloroacetic acid (327 mg, 2 mmol) were consecutively added. The mixture was stirred at r.t. for 3 d, cooled at 0 °C overnight, then filtered, and the collected solid was recrystallized from MeOH, from which product **6e** was obtained as colorless crystals (347 mg, 68%); mp 210–212 °C (MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.73–1.28 (m, 5 H), 1.65–1.41 (m, 5 H), 2.34 (s, 3 H), 2.42 (s, 3 H), 3.50–3.61 (m, 1 H), 6.10 (d, *J* = 7.8 Hz, 1 H), 6.27 (s, 1 H), 7.10 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.86 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (Me), 21.8 (Me), 24.4 (CH_2), 24.5 (CH_2), 25.3 (CH_2), 32.0 (CH_2), 32.3 (CH_2), 48.6 (CH), 71.1 (CH), 93.0 (C_q), 127.8 (C_q), 128.5 (CH_{Ar}), 129.0 (CH_{Ar}), 129.6 (CH_{Ar}), 131.2 (CH_{Ar}), 132.9 (C_q), 135.8 (C_q), 139.7 (C_q), 145.2 (C_q), 161.1 (C_q), 162.8 (C_q), 194.1 (C_q). IR (KBr): 3242, 1771, 1631, 744 cm^{-1}. MS (EI): *m*/*z* (%) = 512 (0.7) [M^+ + 4], 510 (3.4) [M^+ + 2], 508 (2.5) [M^+], 391 (27), 390 (100), 307 (45), 119 (92). HRMS (EI): *m*/*z* calcd for $C_{25}H_{27}Cl_3N_2O_3$: 508.1056; found: 508.1087. Anal. Calcd for $C_{25}H_{27}Cl_3N_2O_3$: C, 58.89; H, 5.34; N, 5.49. Found: C, 58.83; H, 5.28; N, 5.43.