Kinetics and mechanism of the aminolysis of *S*-phenyl cyclopropanecarboxylates in acetonitrile

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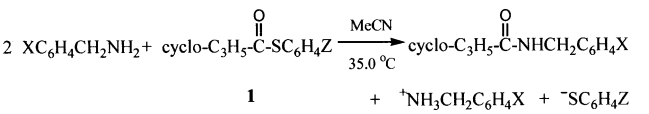
The kinetics and mechanism of the aminolysis of *S*-phenyl cyclopropanecarboxylates [*cyclo*-$C_3H_5C(=O)$-SC_6H_4Z] with benzylamines ($XC_6H_4CH_2NH_2$) were investigated in acetonitrile at 35.0 °C. The large magnitudes of the Brönsted coefficients β_X (1.7–2.3) and β_Z (−0.9 to −1.3), together with a large positive cross-interaction constant $\rho_{XZ} = +1.4$, are interpreted to indicate a stepwise mechanism with rate-limiting breakdown of the zwitterionic tetrahedral intermediate, $T^{\pm}$. The proposed mechanism is supported by adherence of the rates to the reactivity-selectivity principle (RSP). The kinetic isotope effects involving deuterated benzylamines ($XC_6H_4CH_2ND_2$) are greater than unity ($k_H/k_D > 1.0$), suggesting the possibility of a hydrogen-bonded four-center transition state. The activation parameters, $\Delta H^{\neq}$ (≅5 kcal mol^{-1}) and $\Delta S^{\neq}$ (= −45 to −54 e.u.), are consistent with this transition state structure.

The mechanisms of the aminolysis of aryl esters[1] and carbonates,[2] and their thiol, thiono and dithio derivatives,[3] have been extensively studied. Curved Brönsted plots in the aminolysis reactions have been interpreted in terms of a zwitterionic tetrahedral intermediate, $T^{\pm}$, in the reaction path and a change in the rate-limiting step from leaving group expulsion to attack by the nucleophile as the nucleophile becomes more basic.[4] In some of the cases, however, the aminolysis has been found to proceed concertedly in a single step through a tetrahedral transition state (TS).[4,5] The mechanistic change from a stepwise mechanism through an intermediate, $T^{\pm}$, to a concerted one *via* a single TS has been reported to be caused by destabilization of the tetrahedral intermediate, $T^{\pm}$, due to several factors, including enhanced leaving ability of the leaving group (LG),[5d,e] strong electronic push provided by the substrate (nonleaving group)[5a,b] and destabilization rendered by the amines and by substitution of S^- by O^- [5b] in the tetrahedral intermediate, $T^{\pm}$. For example, the aminolyses of 2,4-dinitrophenyl methyl carbonate with pyridines, anilines and secondary alicyclic amines were found to proceed by a stepwise mechanism.[2d,e] In contrast, however, its thiol analog (MeO and EtO are very similar[6,7]) was found to react by a concerted mechanism with secondary alicyclic amines[5a,b] due to destabilization of the TS by the enhanced leaving ability of ArS^- relative to ArO^-. For aminolysis of ethyl *S*-aryl thiolcarbonates, the mechanism also changes from stepwise to concerted when Ar is changed from 4-NO_2Ph to 2,4-$(NO_2)_2$Ph and 2,4,6-$(NO_2)_3$Ph with quinuclidine bases,[5d] and also when Ar is changed from 2,4-$(NO_2)_2$Ph to 2,4,6-$(NO_2)_3$Ph with anilines.[5e] These results show that although the EtO (and MeO) group is conducive to a concerted process, the mechanism is also sensitive to the leaving group ability.

In this work, we investigate the kinetics and mechanism of the aminolysis of *S*-*Z*-phenyl cyclopropanecarboxylates (**1**) with X-benzylamines in acetonitrile at 35.0 °C, eqn. (1), where X = *p*-OMe, *p*-Me, H, *p*-Cl and *m*-Cl, and Z = *p*-Me, H, *p*-Cl and *p*-Br.



(1)

The reactions have been conducted under pseudo-first-order conditions with a large excess of amine. The purpose of this work is to elucidate the mechanism by determining various selectivity parameters, ρ_X, β_X, ρ_Z and β_Z, including the cross-interaction constant[8] ρ_{XZ} in eqn. (2), where X and Z are substituents in the nucleophile and leaving group, respectively.

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (2)$$

We are interested in any mechanistic change that may occur due to the change of leaving group from ArO^- to ArS^-.

Results and discussion

The reactions of benzylamine (BA) with *S*-phenyl cyclopropane carboxylates (SPC) under the reaction conditions obey the rate law given by eqns. (3) and (4); k_0 and k_N are the rate constants for solvolysis in MeCN and aminolysis of the substrate, respectively.

$$\text{Rate} = k_{obs} \cdot [\text{SPC}] \quad (3)$$

$$k_{obs} = k_0 + k_N \cdot [\text{BA}] \quad (4)$$

Plots of k_{obs} against benzylamine concentration, [BA], were linear, according to eqn. (4) with a negligible intercept ($k_0 \cong 0.0$) and a slope k_N (M^{-1} s^{-1}), summarized in Table 1. No third-order or high-order terms were detected, and no complications were found in the determination of k_{obs} nor in the linear plots of eqn. (4). This suggests that there is no base-catalysis or noticeable side reactions and the overall reaction

Table 1 The second-order rate constants, $k_N \times 10^3$ M^{-1} s^{-1} of the reactions of *S*-*Z*-phenyl cyclopropanecarboxylates with X-benzylamines in acetonitrile at 35.0 °C

	Z					
X	*p*-Me	H	*p*-Cl	*p*-Br	ρ_Z[a]	β_Z[b]
p-OMe	20.1	41.7	117	150	2.12 ± 0.08	−0.86 ± 0.06
	14.2[c]			105		
	9.94[d]			75.6		
p-Me	11.4	26.1	89.4	111	2.43 ± 0.12	−1.00 ± 0.05
H	4.78	12.0	38.7	51.6	2.50 ± 0.06	−1.02 ± 0.08
p-Cl	1.68	4.51	18.2	24.3	2.83 ± 0.11	−1.16 ± 0.07
	1.21[c]			17.7		
	0.883[d]			12.6		
m-Cl	0.581	1.75	8.71	10.7	3.14 ± 0.17	−1.29 ± 0.05
ρ_X[a,e]	−2.32 ± 0.09	−2.09 ± 0.08	−1.76 ± 0.07	−1.74 ± 0.08		
					ρ_{XZ}[f] = 1.44 ± 0.31	
β_X[g]	2.26 ± 0.13	2.04 ± 0.12	1.71 ± 0.11	1.69 ± 0.12		

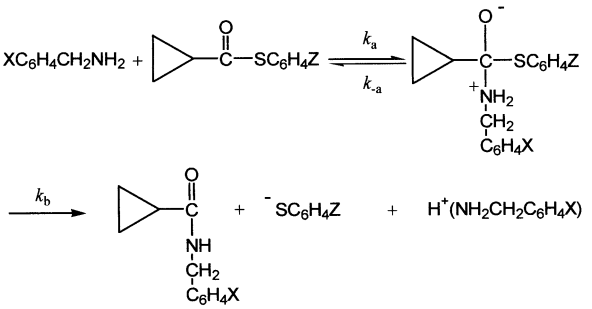
[a] The σ and σ^- values were taken from C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165. Correlation coefficients were better than 0.997 in all cases. [b] The pK_a values were taken from *Dictionary of Organic Chemistry*, ed. J. Buckingham, Chapman and Hall, New York, 5th edn., 1982. An interpolated value of $pK_a = 5.87$ was used for *p*-BrC_6H_4SH. Correlation coefficients were better than 0.994 in all cases. [c] At 25.0 °C. [d] At 15.0 °C. [e] Correlation coefficients were better than 0.997 in all cases. [f] Correlation coefficient was 0.997. [g] The pK_a values were taken from A. Fischer, W. J. Galloway and J. Vaughan, *J. Chem. Soc.*, 1964, 3588. Correlation coefficients were better than 0.994 in all cases. $pK_a = 9.67$ was used for X = *p*-CH_3O (H. K. Oh, J. Y. Lee and I. Lee, *Bull. Korean Chem. Soc.*, 1998, **19**, 1198).

follows the route given by eqn. (1). The Hammett coefficients, ρ_X and ρ_Z, and the Brönsted coefficients, β_X (β_{nuc}) and β_Z (β_{lg}), are also collected in Table 1, together with the cross-interaction constant ρ_{XZ}.

As we have pointed out previously, the Brönsted slopes obtained by plotting $\log k_N$(MeCN) *vs.* $pK_a(H_2O)$ are justified[9] since the pK_a(MeCN) values are found to vary in parallel with the $pK_a(H_2O)$ values for structurally similar amines. Since we found that the Brönsted slopes for the plots of $\log k_N$(MeCN) *vs.* $pK_a(H_2O)$ of pyridines are somewhat larger than those for the plots of $\log k_N$(MeCN) *vs.* pK_a(MeCN) of pyridines in the phosphoryl transfer reactions,[10] the reported magnitude of the β_X values may be somewhat larger than the correct values using pK_a(MeCN). However, the comparison of β_X values in Table 1 with the corresponding values determined using the similar $pK_a(H_2O)$ may be approximately applicable.[9c]

Rates for the aminolysis of *S*-phenyl (–SAr) propanecarboxylates are much faster than the corresponding values for the aminolysis of the phenolate (–OAr) analogs;[1j] for example, for the reaction of the phenolate analog with X = H and Z = 4-CH_3CO ($\sigma_p = +0.50$) k_N is 4.17×10^{-3} M^{-1} s^{-1} at 55.0 °C while for thiophenolate with X = H and Z = 4-Me ($\sigma_p = -0.17$) k_N is 4.78×10^{-3} M^{-1} s^{-1} at 35.0 °C. Note that the former has a lower rate at a higher reaction temperature (by 20 degrees) despite its electron acceptor substituent. Since the nucleophile is the same, benzylamine in both cases, the faster rates of thiophenolates indicate the importance of bond cleavage in the TS, since the thiophenolates used in the present work are weakly basic relative to the phenolates used in the studies and hence are much better leaving groups.

The β_X (β_{nuc}) values are large, ranging from 1.7 to 2.3, which are quite larger than the $\beta_X \geqslant 0.8$–1.0 normally expected for a stepwise mechanism with rate-limiting expulsion of the leaving group (ArS^-) from $T^{\pm}$.[1,2] Similarly the β_Z (β_{lg}) values have also large magnitudes ($\beta_Z = -0.9$ to -1.3), which are again greater than those normally expected from such a mechanism, albeit the exact comparison is difficult due to the use of $pK_a(H_2O)$ for the β_Z determination.[1a,2a] These β_X and β_Z values strongly suggest a stepwise mechanism with rate-limiting breakdown of the $T^{\pm}$ intermediate, k_b in eqn. (5),



(5)

where $k_N = (k_a/k_{-a})k_b = K \cdot k_b$. Close examination of these values, however, shows that the magnitude of β_X is somewhat larger with ArS^- ($\beta_X = 1.7$–2.3) than that with ArO^- ($\beta_X = 1.3$–2.1), while that of β_Z is smaller ($\beta_Z = -0.9$ to -1.3) than that for ArO^- [1j] ($\beta_Z = -1.1$ to -1.4). The differences are small, but the trends are clear. These trends reflect that the TS with ArS^- is somewhat tighter than that with ArO^-, as evidenced by a larger positive cross-interaction constant ρ_{XZ} (1.4 *vs.* 1.1).[8] We therefore conclude that the enhanced leaving ability from substitution of ArO^- by ArS^- causes no mechanistic change but leads to a somewhat tighter TS.

Table 2 Kinetic isotope effects in the reactions of *S*-*Z*-phenyl cyclopropanecarboxylates with deuterated X-benzylamines in acetonitrile at 35.0 °C

X	Z	$k_H \times 10^3/M^{-1}$ s^{-1}	$k_D \times 10^3/M^{-1}$ s^{-1}	k_H/k_D
p-OMe	*p*-Me	20.1 ± 0.2	14.6 ± 0.2	1.38 ± 0.02[a]
p-OMe	H	41.7 ± 0.9	31.8 ± 0.7	1.31 ± 0.04
p-OMe	*p*-Cl	117 ± 2	93.6 ± 0.2	1.25 ± 0.03
p-OMe	*p*-Br	150 ± 3	124 ± 2	1.21 ± 0.04
p-Cl	*p*-Me	1.68 ± 0.02	1.17 ± 0.01	1.43 ± 0.02
p-Cl	H	4.51 ± 0.05	3.24 ± 0.03	1.39 ± 0.02
p-Cl	*p*-Cl	18.2 ± 0.2	13.8 ± 0.2	1.32 ± 0.03
p-Cl	*p*-Br	24.3 ± 0.3	19.3 ± 0.3	1.26 ± 0.03

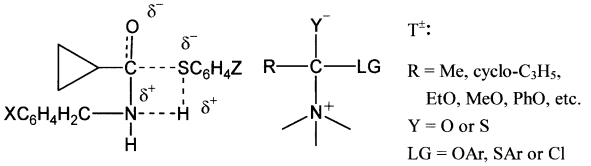
[a] Standard deviations.

Table 3 Activation parameters[a] of the reactions of *S*-*Z*-phenyl cyclopropanecarboxylates with X-benzylamines in acetonitrile

X	Z	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	5.6	48
p-OMe	*p*-Br	5.4	45
p-Cl	*p*-Me	5.1	54
p-Cl	*p*-Br	5.2	49

[a] Calculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, *Physical Organic Chemistry*, Wiley, New York, 1964, p 378) are ±0.5 kcal mol^{-1} and ±2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively. The levels of confidence are better than 95%. Temperature range is 15.0–35.0 °C.

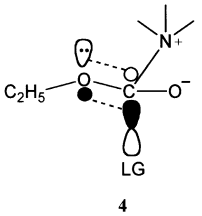
The kinetic isotope effects (k_H/k_D) in Table 2 involving deuterated benzylamine ($XC_6H_4CH_2ND_2$) nucleophiles in acetonitrile are greater than unity ($k_H/k_D = 1.3$–1.4), indicating that the N–H proton transfer takes place in the rate-determining step[8b] so that a four-center-type TS, **2**, is involved.[8b] In this type of TS, hydrogen bonding of an amine hydrogen atom to the departing thiophenoxide facilitates the



2 **3**

rate-limiting bond cleavage step, forming a rather constrained four-membered ring. This is reflected in the low activation enthalpies ($\Delta H^{\neq} \cong 5$ kcal mol^{-1}) and large negative activation entropies ($\Delta S^{\neq} = -45$ to -54 e.u.) in Table 3. The expulsion of the ArS^- anion in the rate-determining step (an endoergic process) is assisted by the hydrogen bonding with an amino hydrogen of the benzylammonium ion within the intermediate, $T^{\pm}$. This will lower the $\Delta H^{\neq}$ value, but the TS becomes structured and rigid (low entropy process), which should lead to a large negative $\Delta S^{\neq}$ value.

It is also notable that the trends in rates and selectivity parameters in Table 1 conform to the reactivity-selectivity principle,[11] which supports our proposed mechanism.[1j,8,12] Here it is appropriate to comment on the factors that destabilize the zwitterionic tetrahedral intermediate, **3** ($T^{\pm}$), and hence are conducive to a concerted aminolysis reaction. (a) The strongest influence comes from the nonleaving group, R in **3**; if this group has an electron donor the leaving group (LG) expulsion is facilitated. However, the enhanced nucleofugality by an electron donor R alone is not enough normally to enforce a concerted aminolysis. When the R group has an oxygen (or nitrogen) with a lone pair (*n*), preferably of the p type, directly attached to the carbonyl carbon as in R = MeO, EtO and PhO, the strong n_O-σ^*_{C-LG} vicinal charge transfer interaction[13] in **3** causes extensive weakening of the C–LG bond to the extent that the intermediate cannot exist. This *n*-σ^* lone pair-antibond, or bond-antibond interaction, is stronger (i) when the lone pair level is higher and the σ^* level is lower, and (ii) the *n* and σ^* have an antiperiplanar conformation,[12] as in **4**. Since the alkyl



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groups, Me and Et, are stronger electron donors, the lone pair level on the oxygen of the alkoxy group, EtO, is raised. PhO is in this sense not as efficient since Ph is an acceptor. (b) On the other hand, an electron withdrawing group such as *p*-NO_2 or *p*-CN on the leaving group depresses the σ^*_{C-LG} level, while the σ^*_{C-S} level is significantly lower than the σ^*_{C-O} level.[13a] (c) The amine expulsion from $T^{\pm}$ in **3** is faster in the order[5d,14] pyridine < aniline < secondary alicyclic amines < primary amines, so that provided other conditions are equal, pyridines are more likely to lead to a stable $T^{\pm}$ and hence a stepwise mechanism, while the secondary alicyclic and primary amines are more likely to lead to a concerted mechanism. (d) The thiono intermediate, with Y = S in **3**, is more stable than the carbonyl counterpart, Y = O, since the C=S bond is weaker than the C=O bond.[3,5b]

In conclusion, a concerted aminolysis is favored by (i) an alkoxy group, R = CH_3O, EtO, *etc.* in **3**, (ii) by a leaving group with a lower σ^*_{C-LG} level, that is $\sigma^*_{C-S} < \sigma^*_{C-O}$, and leaving group (LG) with strong electron-withdrawing substituents, (iii) by primary or secondary amines rather than pyridines, and (iv) by a carbonyl (C=O) rather than thiono (C=S) compound. The strongest contribution comes from a n_O-σ^*_{C-LG} type vicinal charge transfer interaction in the tetrahedral intermediate $T^{\pm}$, due to a strong destabilization caused by the weakening of the C–LG bond. Alkyl groups with $\sigma = -0.04$ to $\sigma = -0.21$ in **3** cannot destabilize the $T^{\pm}$ enough to cause a concerted aminolysis,[1j,k,15] although they are electron donors, due to the lack of *n*-σ^*_{C-LG} type vicinal charge transfer (or anomeric effect), although the amine (benzylamine) and leaving group (ArS^-) are highly conducive to such a single-step nucleophilic displacement.

Experimental

Materials

Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and cyclopropanecarbonyl chloride were Tokyo Kasei GR grade. Preparation of deuterated benzylamine: benzylamine was dissolved in excess D_2O under nitrogen atmosphere and left for 5 h. The deuterated benzylamine was extracted with dry ether and dried again over $MgSO_4$ and then the solvent was removed. This procedure was repeated three times. The anlysis (NMR) of the dried deuterated benzylamine has more than 99% deuterium content and thus the k_H/k_D values were not corrected for the deuterium content.

Preparations of *S*-phenyl cyclopropanecarboxylates

Thiophenol derivatives and cyclopropanecarbonyl chloride were dissolved in anhydrous ether and pyridine carefully added, keeping the temperature at 0–5 °C. Ice was then added to the reaction mixture and the ether layer was separated, dried on $MgSO_4$ and distilled under reduced pressure to remove the solvent. IR (Nicolet 5BX FT-IR) and ^1H and ^{13}C NMR (JEOL 400 MHz) data are given below. A Hewlett Packard quadrupole mass spectrometer with electron impact ionization mode was used to measure MS data and a Perkin Elmer elemental analyzer was used for microanalysis. The yields ranged from from 70 to 95%.

***S*-*p*-Tolyl cyclopropanecarboxylate.** Liquid; IR (KBr) 3013 (C–H, aromatic), 2932 (C–H, CH_3), 1695 (C=O), 1578 (C=C, aromatic) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.25 (4H, m, CH_2), 2.07 (1H, t, CH), 2.35 (3H, s, CH_3), 7.21 (2H, d, $J = 8.30$ MHz, *meta* H), 7.29 (2H, d, $J = 8.30$ MHz, *ortho* H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 207.6 (C=O), 139.4, 134.3,

130.0, 129.2, 22.1, 21.4, 9.14; MS, m/z 192 (M^+). Anal. calcd. for $C_{11}H_{12}OS$: C, 68.7; H, 6.31. Found: C, 68.5; H, 6.33.

***S*-Phenyl cyclopropanecarboxylate.** Liquid; IR (KBr) 3013 (C–H, aromatic), 1695 (C=O), 1578 (C=C, aromatic) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.25 (4H, m, CH_2), 2.05 (1H, t, CH), 7.34–7.43 (5H, m, aromatic); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 197.2 (C=O), 134.3, 129.1, 128.8, 127.7, 21.0, 14.2; MS m/z 178 (M^+). Anal. calcd. for $C_{10}H_{10}OS$: C, 67.4; H, 5.71. Found: C, 67.6; H, 5.69.

***S*-*p*-Chlorophenyl cyclopropanecarboxylate.** Liquid; IR (KBr) 3013 (C–H, aromatic), 1695 (C=O), 1578 (C=C, aromatic) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.23 (4H, m, CH_2), 2.08 (1H, t, CH), 7.32 (2H, d, $J = 8.78$ MHz, *meta* H), 7.38 (2H, d, $J = 9.22$ MHz, *ortho* H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 196.6 (C=O), 135.6, 135.5, 129.1, 126.2, 22.3, 11.4; MS m/z 212 (M^+). Anal. calcd. for $C_{10}H_9ClOS$: C, 56.5; H, 4.32. Found: C, 56.7; H, 4.34.

***S*-*p*-Bromophenyl cyclopropanecarboxylate.** Liquid; IR (KBr) 3013 (C–H, aromatic), 1695 (C=O), 1578 (C=C, aromatic) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.25 (4H, m, CH_2), 2.07 (1H, t, CH), 7.27 (2H, d, $J = 8.30$ MHz, *meta* H), 7.53 (2H, d, $J = 8.30$ MHz, *ortho* H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 196.4 (C=O), 135.7, 132.1, 126.8, 123.8, 22.4, 11.4; MS m/z 257 (M^+). Anal. calcd. for $C_{10}H_9BrOS$: C, 46.7; H, 4.51. Found: C, 46.9; H, 4.49.

Kinetic measurements

Rates were measured conductometrically at 35.0 ± 0.05 °C. The apparatus used in this work was a home-built computer automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method[16] with a large excess of benzylamine. [Substrate] $\cong 10^{-3}$ M; [BA] $= 0.2–7 \times 10^{-1}$ M. Second-order rate constants, k_N, were obtained from the slope of a plot of k_{obs} *vs.* benzylamine with more than five concentrations and were reproducible to within $\pm 3\%$.

Product analysis

S-Phenyl cyclopropanecarboxylate (0.05 mole) and *p*-chlorobenzylamine (0.5 mole) were added to acetonitrile and reacted at 35.0 °C under the same conditions as for the kinetic measurements. After more than 15 half lives, the solvent was removed under reduced pressure and the product separated by column chromatography (silica gel, 10% ethylacetate–*n*-hexane). Analysis of the product gave the following results.

***cyclo*-$C_3H_5C(=O)NHCH_2C_6H_4Cl$.** m.p. 147–149 °C; IR (KBr) 3284 (N–H), 3001 (C–H, CH_2), 2975 (C–H, benzyl), 2943 (C–H, CH_3), 1685 (C=O), 1549 (C=C, aromatic), 825 (C–H, aromatic) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.764 (2H, dt, cyclopropane), 1.01 (2H, dt, cyclopropane), 1.31–1.36 (1H, m, CH), 4.40 (2H, d, NH–CH_2), 7.21–7.20 (2H, d, aromatic ring, *meta*, $J = 8.30$ Hz), 7.23–7.27 (2H, d, aromatic ring, *ortho*, $J = 8.30$ Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 175.8 (C=O), 173.4, 136.9, 133.2, 129.1, 128.7, 43.1, 14.8, 7.42; MS m/z 209 (M^+). Anal. calcd. for $C_{11}H_{12}ClNO$: C, 63.0; H, 5.81. Found: C, 63.2; H, 5.83.

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