Kinetics and mechanism of the aminolysis of phenyl cyclopropanecarboxylates in acetonitrile

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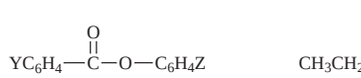
Kinetic studies of the reaction of Z-phenyl cyclopropanecarboxylates with X-benzylamines in acetonitrile at 55.0 °C have been carried out. The reaction proceeds by a stepwise mechanism in which the rate-determining step is the breakdown of the zwitterionic tetrahedral intermediate, $T^{\pm}$, with a hydrogen-bonded four-center type transition state (TS). These mechanistic conclusions are drawn based on (i) the large magnitude of ρ_X and ρ_Z, (ii) the normal kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated benzylamine nucleophiles, (iii) the positive sign of ρ_{XZ} and the larger magnitude of ρ_{XZ} than that for normal S_N2 processes, and lastly (iv) adherence to the reactivity–selectivity principle (RSP) in all cases.

Introduction

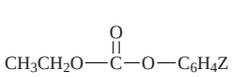
Aminolyses of ester compounds have been the subject of numerous kinetic studies.[1–3] Most of these reactions are nucleophilic and in some of them curved Brønsted-type plots have been found, which have been explained by the existence of at least one tetrahedral intermediate in the reaction path and a change in the rate-determining step.[2]

In contrast to the generally accepted view of the past 20–30 years that nucleophilic substitution reactions at a carbonyl group involve almost invariably the tetrahedral intermediate, it has been shown recently that some acyl transfer reactions can involve a concerted mechanism.[4] Most of these studies are, however, carried out in protic solvents, typically in aqueous solution. Recent results of aminolysis studies of esters[5] and acyl halides[2a,6] have shown that the similar mechanism involving the tetrahedral intermediate also applies in aprotic solvents like acetonitrile.

The reactions of Z-phenyl Y-benzoates (**I**),[1b] ethyl Z-phenyl carbonates (**II**)[1i] and Z-phenyl 2-furoates (**III**)[1g] with X-benzylamines in acetonitrile at 55.0 °C have been found to proceed *via* a tetrahedral intermediate, $T^{\pm}$, with its breakdown as the rate-determining step.



I



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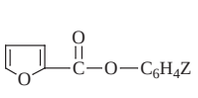
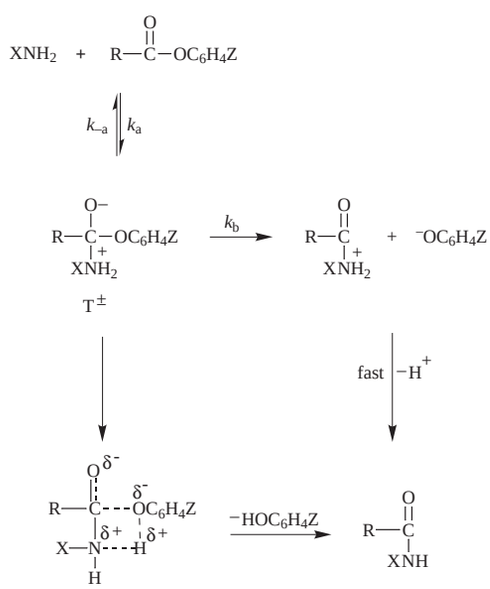


III

The following mechanistic criteria are proposed theoretically[7] and found experimentally[1–5] to apply to the stepwise mechanism with rate-limiting expulsion of the leaving group in the aminolysis of esters and carbonates. (i) The magnitudes of the reaction constants ρ_X (ρ_{nuc}) and ρ_Z (ρ_{lg}) [and also the corresponding β_X (β_{nuc}) and β_Z (β_{lg})] values, based on the macroscopic rate constants, $k_2 = (k_a/k_{-a})k_b = Kk_b$ for the simplified reaction given by Scheme 1, are large.[1,7] (ii) The signs of cross-interaction constants, ρ_{ij} in eqn. (1),[8] where i and j are the substituents on the nucleophile (X), the substrate (Y) or the leaving group (Z), are opposite ($\rho_{XY} > 0$ and $\rho_{YZ} < 0$)[1,7] to those for normal S_N2 processes or for acyl transfers with rate-limiting formation of the tetrahedral intermediate, $T^{\pm}$ ($\rho_{XY} > 0$ and $\rho_{YZ} < 0$). The sign of ρ_{XZ} is always positive in the stepwise mechanism with rate-limiting decomposition of the tetrahedral intermediate, $T^{\pm}$, (Scheme 1), whereas in the concerted S_N2 reactions it can be either positive or negative.[1,8] (iii) The magnitudes of ρ_{XY}, ρ_{YZ} and ρ_{XZ} are greater than those for normal S_N2 processes.[1,8] (iv) The deuterium kinetic isotope effects involving deuterated nucleophiles are normal, $k_H/k_D > 1.0$.[1,5,8] (v) The RSP holds, *i.e.* a faster rate is accompanied by a lower selectivity.[9] (vi) There is a small positive enthalpy of activation, $\Delta H^{\ddagger}$, and a large negative entropy of activation, $\Delta S^{\ddagger}$.[1e,2c,10]



Scheme 1

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (1a)$$

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial\sigma_X\,\partial\sigma_Z} = \frac{\partial\rho_Z}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Z} \quad (1b)$$

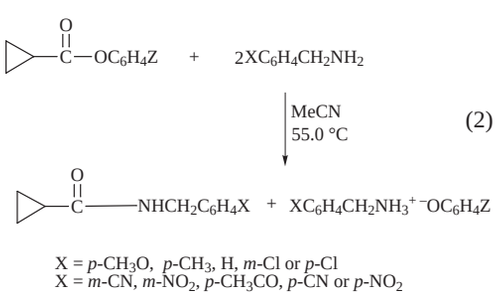
Table 1 Second-order rate constants, k_N (10^3 dm^3 mol^{-1} s^{-1}), for the reactions of Z-phenyl cyclopropanecarboxylates with X-benzylamines in acetonitrile at 55.0 °C

	Z						
X	*m*-CN	*m*-NO_2	*p*-CH_3CO	*p*-CN	*p*-NO_2	ρ_Z[a]	β_Z[b]
p-CH_3O	2.09	5.01	15.1	20.1	116 (30.2)[c]	2.41 ± 0.08	−1.10
p-CH_3	1.23 0.911[d] 0.675[e]	2.95	7.41	15.1	70.8 52.8 39.4 (27.5)	2.47 ± 0.01	−1.10
H	0.562	1.41	4.17	7.08	54.1 (22.9)	2.75 ± 0.06	−1.27
p-Cl	0.170	0.447	1.58	2.88	23.4 (16.2)	2.99 ± 0.06	−1.37
m-Cl	0.0977 0.0688 0.0485	0.288	0.832	2.01	14.4 10.4 7.56	2.97 ± 0.02	−1.35
ρ_X[f]	−2.10 ± 0.02	−1.97 ± 0.04	−1.88 ± 0.05	−1.63 ± 0.04	−1.36 ± 0.05	ρ_{XZ}[g] = 1.06 ± 0.17	
β_X[h]	2.09 ± 0.02	1.94 ± 0.03	1.78 ± 0.03	1.66 ± 0.04	1.33 ± 0.05		

[a] The σ^- values were taken from H. H. Jaffe, *Chem. Rev.*, 1953, **53**, 191. Correlation coefficients were better than 0.994 in all cases. [b] The pK_a values were taken from A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, 3rd edn., 1984, p. 45. Correlation coefficients were better than 0.976 in all cases. Z = *p*-CH_3CO and *m*-CN were excluded. [c] The values in parentheses are those for the corresponding reactions of phenyl benzoates. [d] At 45.0 °C. [e] At 35.0 °C. [f] The σ values were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420. Correlation coefficients were better than 0.994 in all cases. [g] Correlation coefficient was 0.997. [h] 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 0.992 in all cases. X = *p*-CH_3O were excluded from the Brønsted plot for β_X (benzylamine) due to an unreliable pK_a value listed.

Besides a change in the reaction medium from protic to aprotic, a change in the acyl group (R) to a stronger electron acceptor is also known to favor the stepwise mechanism with rate-limiting decomposition of the tetrahedral intermediate, $T^{\pm}$ (Scheme 1).[2b,7,11]

In the present work we carried out a kinetic and mechanistic study of the reactions of cyclopropanecarboxylate with benzylamines in acetonitrile at 55.0 °C. We varied the two substituents X and Z on the nucleophile and leaving group, respectively [eqn. (2)].



Not much is known about the aminolysis of small ring cyclo ester compounds. Therefore, kinetic studies have been carried out in order to clarify the mechanism of the reactions of the cyclopropyl ester compounds. To our knowledge there have been no reports of the kinetics of the aminolysis of phenyl cyclopropanecarboxylates.

Results and discussion

The reactions were first-order (k_{obs}) in both benzylamine, [N], and substrates, [S], eqns. (3) and (4), under the experimental

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

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

conditions. Plots of k_{obs} against benzylamine concentration were linear in accordance with eqn. (4), where k_0 and k_N are the rate coefficients for solvolysis and aminolysis, respectively, of the phenyl cyclopropanecarboxylates. The solvolysis was not observed under the reaction conditions ($k_0 \cong 0$). The second-order rate constants for aminolysis (k_N) were obtained from the slopes of the plots [eqn. (4)]. These values, together with the Hammett [$\rho_X(\rho_{nuc})$ and $\rho_Z{}^-(\rho_{lg}{}^-)$] and Brønsted [$\beta_X$ (β_{nuc}) and β_Z (β_{lg})] coefficients, are shown in Table 1.

Rates are faster with a stronger nucleophile ($\delta\sigma_X < 0$) and nucleofuge ($\delta\sigma_Z > 0$) as is expected from a typical nucleophilic substitution reaction. The rates are ~2–3 times faster than those for phenyl benzoates[1b] (given in parentheses) under the same reaction conditions. This could be due to a larger electron donating resonance of the phenyl ring ($\sigma_R = -0.28$)[1g,12] relative to that of the cyclopropane ring ($\sigma_R = -0.15$)[1g,12] in the corresponding substrates.

The results in Table 1 reveal that the magnitude of ρ_X is quite large; it ranges from *ca.* −4 to −6 (the corresponding values are −0.76 to −1.90,[1b] −2.85 to −4.83[1i] and −2.94 to −5.38[1g] for the **I**, **II** and **III** series, respectively) after allowing for a fall-off factor of 2.8[9] for the non-conjugating intervening group CH_2 in benzylamine (relative to aniline). This large magnitude of $\rho_X(\rho_{nuc})$ is also reflected in the similarly large magnitude of $\beta_X(\beta_{nuc})$ = 1.33–2.09 (the corresponding values are 0.25–0.70,[1b] 1.08–1.71[1i] and 1.06–1.83[1g] for the **I**, **II** and **III** series, respectively), although the pK_a values used in the determination of β_X for benzylamines are for those in water, so that the β_X values are not quite reliable. These large magnitudes of ρ_X and β_X are indicative of a stepwise mechanism with a rate-limiting breakdown of a zwitterionic tetrahedral intermediate, $T^{\pm}$[1,3,5] (Scheme 1). The importance of the leaving group departure in the rate-determining step is reflected in the better Hammett correlations with $\sigma_Z{}^-$ than with σ_Z and large magnitude of $\rho_Z{}^-$ (= 2.41–2.97) suggesting a strong negative charge development in the phenoxide leaving group with a relatively large extent of bond cleavage in the TS (β_Z = −1.10 to −1.35). These large $\rho_Z{}^-$ (β_Z) values are again indicative of the stepwise mechanism with a rate-limiting breakdown of a zwitterionic tetrahedral intermediate, $T^{\pm}$ (Scheme 1).[1,3,5]

The k_N values in Table 1 are subjected to multiple regression analysis using eqn. (1). The cross-interaction constant ρ_{XY} obtained was positive and large at 1.06. This provides further strong support for the proposed mechanism.[1,7] Since an elec-

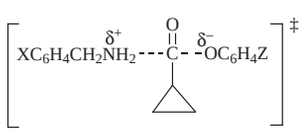
Table 2 Kinetic isotope effects on the second-order rate constants (k_N) for the reactions of Z-phenyl cyclopropanecarboxylates with deuterated X-benzylamines ($XC_6H_4CH_2ND_2$) in acetonitrile at 55.0 °C

X	Z	$k_H/10^3$ dm^3 mol^{-1} s^{-1}	$k_D/10^3$ dm^3 mol^{-1} s^{-1}	k_H/k_D
H	*p*-NO_2	54.1 ± 0.3[a]	44.7 ± 0.3[a]	1.21 ± 0.01[a]
H	*p*-CN	7.08 ± 0.04	5.49 ± 0.05	1.29 ± 0.01
H	*p*-CH_3CO	4.17 ± 0.05	3.16 ± 0.03	1.32 ± 0.02
H	*m*-NO_2	1.41 ± 0.03	1.01 ± 0.006	1.40 ± 0.03
H	*m*-CN	0.562 ± 0.003	0.380 ± 0.006	1.48 ± 0.02
p-CH_3O	*p*-CN	20.1 ± 0.5	16.2 ± 0.4	1.24 ± 0.04
p-CH_3	*p*-CN	15.1 ± 0.2	12.0 ± 0.3	1.26 ± 0.04
p-Cl	*p*-CN	2.88 ± 0.04	2.15 ± 0.03	1.34 ± 0.03
m-Cl	*p*-CN	2.01 ± 0.03	1.46 ± 0.03	1.38 ± 0.04

[a] Standard deviation.

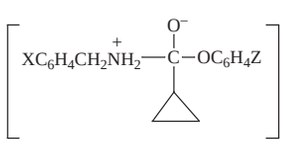
tron acceptor in the nucleophile, $\delta\sigma_X > 0$ (and in the nucleofuge, $\delta\sigma_Z > 0$) leads to an increase in ρ_Z, $\delta\rho_Z > 0$ ($\delta\rho_X > 0$), ρ_{XZ} is positive [eqn. (1*b*)]. We note that the rate increase is invariably accompanied by a decrease in the magnitude of ρ (ρ_X or ρ_Z), and hence the RSP holds.[9,14] Adherence to the RSP is considered another criterion for the stepwise mechanism with rate-limiting expulsion of the leaving group (phenoxides).[9,14]

We determined kinetic isotope effects (k_H/k_D) in acetonitrile for the reactions of Z-phenyl cyclopropanecarboxylates with X-benzylamines deuterated on the nitrogen ($XC_6H_4CH_2ND_2$) (Table 2). We note that the k_H/k_D values are all greater than one, $k_H/k_D > 1.0$, indicating that the rate-determining step is not a simple concerted S_N2 process (**TS1**), or a stepwise mechanism



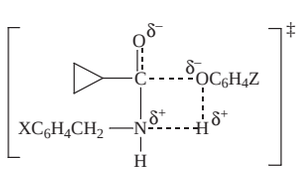
TS1

with a rate-limiting formation of a tetrahedral intermediate (**TS2**) since in such cases inverse kinetic isotope effect, k_H/k_D, are



TS2

expected due to an increase in the N–H vibrational frequency as a result of steric congestion of the N–H moiety in the bond making step. The kinetic isotope effects observed, $k_H/k_D = 1.21$–1.48, are larger than those expected from a stepwise acyl transfer mechanism, but are smaller than normal primary kinetic isotope effects.[1] Close examination of the data in Table 2 reveals that the k_H/k_D values are smaller for a stronger nucleophile and nucleofuge. Since in the intermediate, $T^{\pm}$, both a stronger nucleophile and nucleofuge facilitate the leaving group departure, less assistance is needed in the rate-limiting leaving group departure by the hydrogen bonding of the amine hydrogen.[1f,h,6c] In addition, they also attest to the adherence to the RSP, *i.e.* a faster rate (by a stronger nucleophile and/or nucleofuge) leads to a lower selectivity, k_H/k_D.[9] We therefore conclude that the TS is of a four-center type (**TS3**) in which hydrogen bonding of an amine hydrogen atom occurs to the departing phenoxide.



TS3

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

X	Z	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
p-CH_3	*m*-CN	5.39 ± 0.01	56 ± 1
p-CH_3	*p*-NO_2	6.50 ± 0.01	44 ± 1
m-Cl	*m*-CN	6.41 ± 0.02	58 ± 1
m-Cl	*p*-NO_2	5.80 ± 0.01	49 ± 1

[a] Calculated by the Eyring equation. Errors shown are standard deviations.

Activation parameters for the reactions of phenyl cyclopropanecarboxylates with benzylamines are shown in Table 3. The values of $\Delta H^{\ddagger}$ $\Delta S^{\ddagger}$ were obtained from the slope and intercept, respectively, of Eyring plots, by least-squares analysis. Although the relatively low positive $\Delta H^{\ddagger}$ and large negative $\Delta S^{\ddagger}$ values are in line with the stepwise mechanism,[1e,2c,10] they can also be interpreted as supportive of a concerted mechanism.

Castro *et al.*[15] have argued and Lee *et al.* have shown theoretically[7c] that a tetrahedral intermediate cannot be formed for a substrate with a strong electron donor acyl group, *i.e.* C_2H_5O, due to the kinetic instability brought about by the large values of k_a and k_b[2k,m,15] (Scheme 1). Thus a concerted mechanism is enforced.[2k,m,15] However, for the reaction systems investigated in this work, the cyclopropane group has a relatively low resonance donor effect ($\sigma_R = -0.15$ *vs.* -0.44 for C_2H_5O group)[12] so that the $T^{\pm}$ intermediate seems to be stable enough to lead to the proposed stepwise mechanism.

In summary, the reactions of phenyl cyclopropanecarboxylates with benzylamines in acetonitrile proceed by a stepwise mechanism in which the rate-determining step is the breakdown of the zwitterionic tetrahedral intermediate with a hydrogen-bonded four-center type TS.

These mechanistic conclusions are drawn based on (i) the large magnitude of ρ_X and ρ_Z, (ii) the normal kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated benzylamine nucleophiles, (iii) a small positive enthalpy of activation, $\Delta H^{\ddagger}$, and a large negative entropy of activation, $\Delta S^{\ddagger}$, (iv) the positive sign of ρ_{XZ} and the larger magnitude of ρ_{XZ} than that for normal S_N2 processes, and lastly (v) adherence to the RSP in all cases.

Experimental

Materials

Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Preparation of deuterated benzylamines were as described previously.[1] The analysis (NMR and GC mass spectroscopy) of the deuterated benzylamines showed more than 99% deuterium content, so that no corrections to kinetic isotope effects for incomplete deuteration were made. *J* values are given in Hz. Phenyl cyclopropanecarboxylates

were prepared by reacting phenols with cyclopropanecarbonyl chloride. The substrates synthesized were confirmed by spectral analyses as follows.

***p*-Cyanophenyl cyclopropanecarboxylate.** Mp 41–42 °C; δ_H(400 MHz, $CDCl_3$), 7.68 (2H, d, *m*-H, *J* 8.79), 7.24 (2H, d, *o*-H, *J* 8.80), 1.82–1.89 (1H, m, CH), 1.05–1.21 (4H, m, $2CH_2$); ν_{max}(KBr)/cm^{-1} 2900 (CH, aromatic), 2300 (CN), 1720 (C–O); *m*/*z* = 187 (M^+) (Calc. for $C_{11}H_9NO_2$: C, 65.8; H, 4.80. Found: C, 65.7; H, 4.81%).

***m*-Cyanophenyl cyclopropanecarboxylate.** Mp 41–42 °C; δ_H(400 MHz, $CDCl_3$), 7.69 (1H, d, *p*-H, *J* 8.70), 7.60 (1H, t, *o*-H, *J* 2.20), 7.29 (1H, t, *m*-H, *J* 8.06), 7.20 (1H, d, *o*-H, *J* 5.86), 1.82–1.89 (1H, m, CH), 1.05–1.21 (4H, m, $2CH_2$); ν_{max}(KBr)/cm^{-1} 2900 (CH, aromatic), 2300 (CN), 1720 (C=O); *m*/*z* = 187 (M^+) (Calc. for $C_{11}H_9NO_2$: C, 65.8; H, 4.80. Found: C, 65.7; H, 4.79%).

***p*-Nitrophenyl cyclopropanecarboxylate.** Mp 102–103 °C; δ_H(400 MHz, $CDCl_3$), 7.68 (2H, d, *m*-H, *J* 8.79), 7.24 (2H, d, *o*-H, *J* 8.80), 1.83–1.89 (1H, m, CH), 1.04–1.22 (4H, m, $2CH_2$), ν_{max}(KBr)/cm^{-1} 2900 (CH, aromatic), 1720 (C=O); *m*/*z* = 207 (M^+) (Calc. for $C_{10}H_9NO_4$: C, 58.0; H, 4.35. Found: C, 58.1; H, 4.36%).

***m*-Nitrophenyl cyclopropanecarboxylate.** Mp 52–53 °C; δ_H(400 MHz, $CDCl_3$), 8.10 (1H, d, *p*-H, *J* 8.06), 8.01 (1H, *o*-H, *J* 2.20), 7.55 (1H, t, *m*-H, *J* 8.06), 7.46 (1H, d, *o*-H, *J* 5.86), 1.83–1.89 (1H, m, CH), 1.04–1.22 (4H, m, $2CH_2$), ν_{max}(KBr)/cm^{-1} 2900 (CH, aromatic), 1720 (C=O); *m*/*z* = 207 (M^+) (Calc. for $C_{10}H_9NO_4$: C, 58.0; H, 4.35. Found: C, 58.1; H, 4.36%).

***p*-Acetylphenyl cyclopropanecarboxylate.** Mp 91–92 °C; δ_H(400 MHz, $CDCl_3$), 7.98 (2H, d, *m*-H, *J* 8.06), 7.20 (2H, d, *o*-H, *J* 8.79), 2.60 (3H, s, CH_3), 1.83–1.88 (1H, m, CH), 1.03–1.21 (4H, m, $2CH_2$); ν_{max}(KBr)/cm^{-1} 2900 (CH, aromatic), 1720 (C=O); *m*/*z* = 204 (M^+) (Calc. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.88. Found: C, 70.7; H, 5.86%).

Rate constants

Rates were measured conductimetrically at 55.0 ± 0.05 °C. The conductivity bridge used in this work was a self-made 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; [phenyl cyclopropanecarboxylate] 1×10^{-3} M and [benzylamine] = 0.030–0.40 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 of more than three runs and were reproducible to within ±3%.

Product analysis

p-Nitrophenyl cyclopropanecarboxylate was reacted with excess *p*-methylbenzylamine with stirring for more than 15 half-lives at 55.0 °C in acetonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was separated by column chromatography (silica gel, 20% ethyl acetate–*n*-hexane). Analysis of the product gave the following results.

Cyclopropyl-C(O)NHCH$_2$C$_6$H$_4$-*p*-CH$_3$. Mp 141–142 °C; δ_H(400 MHz, $CDCl_3$), 7.13–7.18 (4H, m, aromatic), 5.86 (1H, br s, NH), 4.40 (2H, s, CH_2), 2.33 (3H, s, CH_3), 1.65–1.69 (1H, m, CH), 0.73–1.32 (4H, m, $2CH_3$); ν_{max}(KBr)/cm^{-1} 3200 (NH), 2900 (CH, aromatic), 1720 (C=O); *m*/*z* = 189 (M^+) (Calc. for $C_{12}H_{15}NO$: C, 76.2; H, 7.94. Found: C, 76.3; H, 7.95%).

Acknowledgements

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