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Rearrangement of 5-phenylthiazolidine-2,4-diones to chiral α-ketoamides via α-elimination

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ABSTRACT

An unexpected reaction took place when 5-phenylthiazolidine-2,4-diones were treated in basic media to produce phenyl-α-ketoamides in good yields. The 5-phenylthiazolidine-2,4-diones used as reactants were achieved through a rearrangement, which took place in the corresponding *N*-acyloxazolidinethiones.

α-Ketoamides have received interest because of their variable biological activities[1] and their applications in the elaboration of important heterocycles.[2] Different methods for their preparation have recently been reviewed by Masson and Zhu.[3] In particular, they described a one-pot directed synthesis of alkyl- and aryl α-ketoamides by a $ZnCl_2$-promoted formal oxidative coupling of aldehydes and isocyanides. Chiral α-ketoamides have been used for the preparation of important reagents in asymmetric synthesis, such as α-cyano-α-fluorophenylacetic acid (CFPA)[4] and (*R*)-α-hydroxyphenylacetic acid.[5]

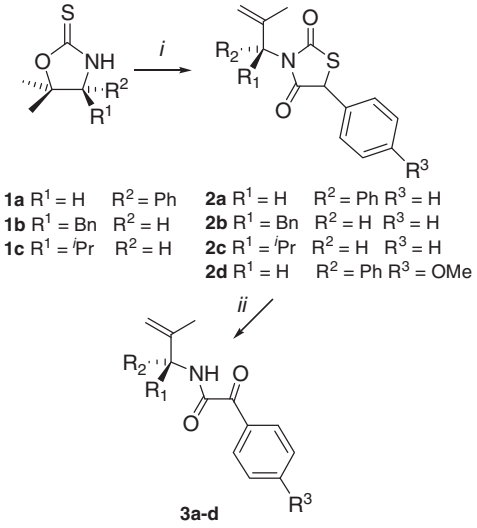
On the other hand, *N*-substituted-thiazolidine-2,4-dione, 5-methylthiazolidine-2,4-dione, and 1,3-thiazinane-2,4-dione were achieved through rearrangement of oxazolidinethiones when reacted with acyl halides and sodium hydride. During this rearrangement an unusual elimination reaction showed: one methyl group of the oxazolidinethione moiety was converted into a terminal alkene. These heterocycles are of synthetic utility for the preparation of chiral allyl ureas, 1,3-amino alcohols, and α-methyl β-aminoacids.[6]

We report herein, on the formation of chiral phenyl α-ketoamides **3a–d**[18–21] from an unexpected reaction that took place when 5-phenylthiazolidine-2,4-diones **2a–d**[14–17] were exposed to basic media. 5-Phenylthiazolidine-2,4-diones **2a–d** were prepared by the above described rearrangement of oxazolidinethiones **1a–c** when reacted with α-chlorophenylacetyl chloride and α-chloro-*p*-methoxiphenylacetyl chloride[7] in the presence of sodium hydride, as shown in Scheme 1.

Oxazolidinethiones[8] **1a–c** were treated with NaH in CH_2Cl_2 followed by dropwise addition of racemic α-chlorophenylacetyl chloride or α-chloro-*p*-methoxiphenylacetyl chloride at 0 °C. After stirring for 1 h at room temperature the reaction was quenched with aq NH_4Cl and washed with saturated aq $NaHCO_3$ and brine. Subsequent extraction with DCM (3×20 ml) and evaporation afforded the N-substituted 5-phenylthiazolidine-2,4-diones **2a–d** as diastereomeric mixtures in moderate yields (50–80%), as shown in Scheme 2 and Table 1.

With the exception of **2a**, which is solid, thiazolidinediones **2b–d** are dense liquids.

For the formation of 5-phenylthiazolidine-2,4-diones **2a–d**, the aqueous solution of $NaHCO_3$ plays an important role. In the absence of $NaHCO_3$ solution, the predominant products are the respective diastereomeric mixtures of *N*-acyl oxazolidinethiones. This is illustrated by the following example: when treating compound **1a** under the reaction conditions described above without using $NaHCO_3$, *N*-acyloxazolidinethione **4a** was obtained as diastereomeric mixture in 80% yield. However, purification of *N*-acylox-



Scheme 1. Reagents and conditions: (i) NaH, PhCHClCOCl or *p*-MeOPhCHClCOCl, 0 °C CH_2Cl_2, aq $NaHCO_3$; (ii) base (1.5 equiv).

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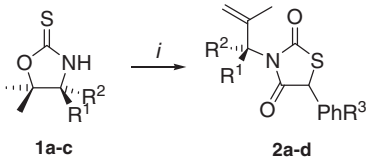
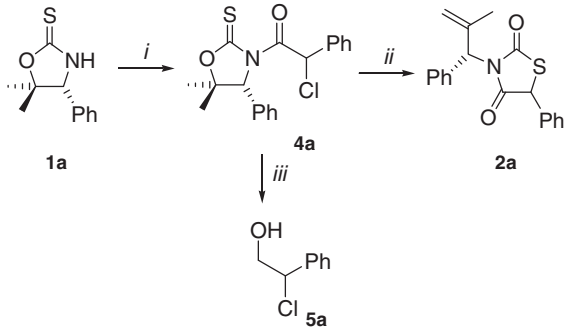


Scheme 2. Reagents and conditions: (i) NaH, α-PhCHClCOCl or *p*-MeOPhCHClCOCl, 0 °C, CH_2Cl_2, aq $NaHCO_3$.

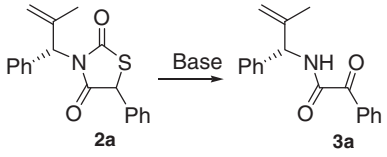
Table 1
Conversion of oxazolidinethiones to 5-phenylthiazolidine-2,4-diones

Entry	Product	R^1	R^2	R^3	Yield[a] (%)
1	**2a**	H	Ph	H	87
2	**2b**	Bn	H	H	50
3	**2c**	*i*Pr	H	H	80
4	**2d**	H	Ph	OMe	70

[a] Purified yield corresponding to mixture of diastereomers.



Scheme 3. Reagents and conditions: (i) NaH, PhCHClCOCl, 0 °C, CH_2Cl_2; (ii) column chromatography; (iii) $NaBH_4$, THF/H_2O.



Scheme 4. Reaction explored in the presence of different bases.

Table 2
Conversion of 5-phenylthiazolidine-2,4-dione **2a** to **3a**

Entry	Base (equiv)	Solvent	*T* (°C)	*t* (h)	Yield (%)
1	NaHMDS (1.5)	THF	−78	4	50
2	KOH (1.5)	THF/H_2O	25	4	85
3	DBU (1.5)	CH_2Cl_2	0	5	50
4	Et_3N (1.5)	CH_2Cl_2	25	4	40
5	DBU (1.5)	CH_2Cl_2	Reflux	4	40

azolidinethione **4a** by column chromatography using silica gel afforded its respective 5-phenylthiazolidine-2,4-dione **2a**. Removal of the chiral auxiliary in compound **4a** was achieved with $NaBH_4$ in THF/H_2O,[9] affording 2-chloro-2-phenylethanol[10] **5a** in 80% yield, as shown in Scheme 3.

An unexpected reaction was observed during the attempt to alkylate compound **2a** with NaHMDS (1.5 equiv) and CH_3I at −78 °C in THF. The reaction mixture gave the chiral phenyl-α-ketoamide **3a** in 50% yield as white solid. This reaction was carried out in the presence of other bases, such as KOH, Et_3N, and DBU. In

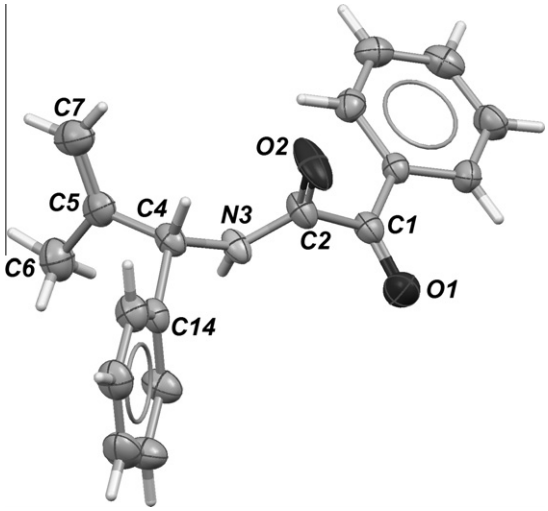
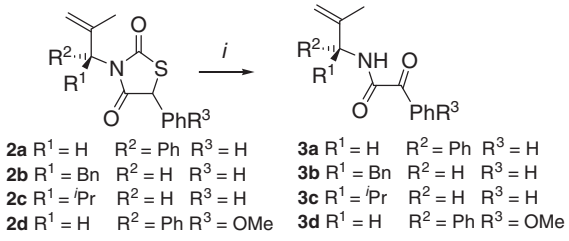


Figure 1. Molecular structure of phenyl-α-ketoamide **3a**. One of the two independent molecules present in the asymmetric unit is shown, with displacement ellipsoids at the 25% probability level.



Scheme 5. Reagents and conditions: (i) KOH (1.5 equiv), THF/H_2O (3:1), 25 °C.

Table 3
Conversion of 5-phenylthiazolidine-2,4-diones to chiral phenyl-α-ketoamides

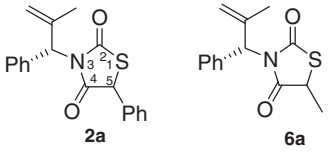
Entry	Product	Yield[a]%	Mp (°C)	$[\alpha]_D^{25}$ (*c*)[b]
1	**3a**	85	127.2	−114.5 (1.3)
2	**3b**	60	72.0	−8.07 (1.0)
3	**3c**	70	93.6	−7.40 (1.0)
4	**3d**	70	Liq	−2.45 (1.0)

[a] Purified yield.
[b] Determined in $CHCl_3$ at 25 °C.

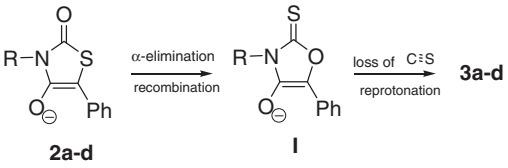
all cases, chiral phenyl-α-ketoamide **3a** was the main product in 40–85% yield. The best yields (85%) were achieved using KOH in THF/H_2O, as shown in Scheme 4 and Table 2 (entry 2).

The structure of compound **3a** was established by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray diffraction analysis[11] (Fig. 1).

An interesting feature figured by **3a** in the solid-state is the fact that this compound crystallizes with two independent molecules in the asymmetric unit, which display dramatically different conformations. Although, both molecules have identical absolute configuration, the allyl and phenyl groups bonded to the chiral C atom



Scheme 6. Thiazolidine-2,4-diones with different substituents at C-5.



Scheme 7. A possible mechanism for the transformation of **2a–d** to **3a–d**.

are free to rotate about C4–C5 and C4–C14 σ-bonds. Such a behavior may have consequences for the reactivity of this class of chiral α-ketoamides in solution.

The rearrangement was explored also for compounds **2b–d** under the same reaction conditions (KOH, THF/H_2O) to give phenyl-α-ketoamides **3b–d** in moderated yields as white solids for **3b–c** and liquid for **3d**, as shown in Scheme 5 and Table 3.

For a successful rearrangement, the presence of the phenyl group at the C5 position of the heterocycle **2a** is essential. If it is replaced by a methyl group, the reaction does not proceed. For example, when treating 5-methylthiazolidine-2,4-dione **6a** under the reaction conditions (KOH, THF/H_2O), only starting material was recovered as shown in Scheme 6.

A possible reaction mechanism could be the following: after deprotonation opening of the cycle occurs via an α-elimination,[13] followed by recombination and cyclization, giving intermediate (I). Finally a loss of fragment CS takes place, followed by reprotonation to afford the α-ketoamide, as shown in Scheme 7.

In conclusion, we have found an unexpected reaction that takes place when 5-phenylthiazolidine-2,4-diones are treated with base and the corresponding phenyl α-ketoamides were obtained in good yields. It was also found that $NaHCO_3$ plays an important role for the rearrangement of *N*-acyloxazolidinethiones to thiazolidine-2,4-diones.

Acknowledgments

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11. *Crystal data for* **3a**: $C_{18}H_{17}NO_2$, M = 279.33, colorless prism, mp = 127.2 °C, 0.40 × 0.16 × 0.16 mm^3, triclinic, space group $P\bar{1}$, cell parameters a = 8.444(4), b = 9.589(4), c = 9.801(5) Å, α = 90.86(5), β = 102.09(3), γ = 104.25(5)°, Z = Z' = 2, D_c = 1.236 g cm^{-3}. 5238 reflections collected on a Siemens P4 diffractometer at room temp, with the Mo Kα radiation (λ = 0.71073 Å) in the range 2θ = 4–50°, of which 2651 are unique (R_{int} = 0.0485). 387 variables refined: R_1 = 0.052 [1755 data with $I > 2\sigma(I)$] and wR_2 = 0.146 [all data].[12] The absolute configurations of C4 and C24 were deduced from the synthetic route: S-C4, S-C24. Measured Friedel pairs were merged. CCDC-779340 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033.
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14. *3-[(S)-2-Methyl-1-phenylallyl)-5-phenylthiazolidine-2,4-dione* (**2a**). White solid, mp = 118 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.44–7.31 (10H, m, Ph), 5.83 (1H, s, CH–N), 5.23 (1H, s, CH=), 5.22 (1H, s, CH=), 4.78 (1H, s, CHS), 1.82 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.8 (C=O), 170.5 (C=O), 139.8 (C=), 135.8, 134.4, 130.9, 129.4, 129.2, 129.0, 128.9, 128.4, 128.3, 128.1 (Ph), 115.4 (CH_2=), 63.4, (C–N), 52.5 (C–S), 21.2 (CH_3); IR ν_{max}: 2929.9, 1755.4, 1677.9, 1494.9, 1454.0, 1314.9, 1153.2, 697.2 cm^{-1}; EI-HRMS: calculated for $C_{19}H_{17}NO_2S$, 323.0980; found, 323.0970.
15. *3-[(S)-3-Methyl-1-phenybut-3-en-2-yl)-5-phenylthiazolidine-2,4-dione* (**2b**). Dense liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.03 (10H, m, Ph), 6.64 (1H, d, J = 7.2 Hz, CH–N), 5.12 (1H, s, CH=), 5.10 (1H, s, CH=), 5.06 (1H, s, CH=), 4.92 (1H, s, CH=), 3.62 (1H, dd, J = 14.0, 12.0 Hz, CH_aH_b), 3.54 (1H, dd, J = 14.0, 12.0 Hz, CH_bH_a), 3.23 (1H, dd, J = 13.6, 4.8 Hz, CH_aH_b), 3.20 (1H, dd, J = 13.6, 4.8 Hz, CH_bH_a), 1.80 (6H, s, 2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.9, 172.7 (C=O), 170.8, 170.5 (C=O), 140.6, 140.5 (C=), 137.2, 137.1, 134.4, 133.9, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 126.7 (Ph), 113.8, 113.7 (CH_2=), 60.0, 59.3 (C–N), 52.5, 52.0 (C–S), 34.6, 34.1 (CH_2) 21.0, 20.9 (CH_3); IR ν_{max}: 2919.3, 1752.8, 1674.5, 1327.4, 1146.3, 746.6, 696.7 cm^{-1}; FAB-HRMS: calculated for $C_{20}H_{20}NO_2S$, 338.1215; found, 338.1206.
16. *3-[(S)-2,4-Dimethylpent-1-en-3-yl)-5-phenylthiazolidine-2,4-dione* (**2c**). Dense liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.33 (10H, m, Ph), 5.40 (1H, s, CH=), 5.35 (1H, s, CH=), 5.22 (1H, s, CH=), 5.20 (1H, s, CH=), 5.14 (1H, br s, CHS), 5.04 (1H, br s, CHS), 4.28 (1H, d, J = 6.0 Hz, CH–N), 4.24 (1H, d, J = 6.3 Hz, CH-N), 2.86 (1H, m, CH), 1.75 (3H, d, J = 6.9 Hz, CH_3), 1.65 (3H, d, J = 6.0 Hz, CH_3), 1.24 (3H, d, J = 5.7 Hz, CH_3), 1.22 (3H, d, J = 5.7 Hz, CH_3), 0.94 (3H, d, J = 6.6 Hz, CH_3), 0.89 (3H, d, J = 6.6 Hz, CH_3), 0.83 (3H, d, J = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 173.2 (C=O), 171.0, 170.9 (C=O), 140.4, 140.3 (C=), 134.6, 134.4, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 128.0 (Ph), 117.3, 117.2 (CH_2=), 67.4, 67.0 (C–N), 52.3, 52.1 (C–S), 25.4, 25.1 (CH_3), 22.2, 22.1 (CH), 20.7, 20.5 (CH_3), 19.6, 19.4 (CH_3); IR ν_{max}: 2968.8, 1751.4, 1675.0, 1454.3, 1378.0, 1315.9, 1185.7, 1113.7, 911.6, 774.8, 724.9, 694.6 cm^{-1}; EI-HRMS: calculated for $C_{16}H_{19}NO_2S$, 289.1137; found, 289.1130.
17. *3-[(S)-2-Methyl-1-phenylallyl)-5-p-methoxiphenyl-thiazolidie-2,4-dione* (**2d**). Liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.31 (12H, m, Ph), 7.25 (2H, d, J = 8.8 Hz, Ph), 7.22 (2H, d, J = 8.8 Hz, Ph), 6.88 (2H, d, J = 8.4 Hz, Ph), 5.85 (1H, s, CH–N), 5.82 (1H, s, CH–N), 5.20 (1H, s, CHS), 5.17 (1H, s, CHS), 5.15 (1H, s, CH=), 5.11 (1H, s, CH=), 4.78 (1H, s, CH=), 4.73 (1H, s, CH=), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.82 (3H, s, CH_3), 1.76 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 173.0 (C=O), 170.7, 170.6 (C=O), 160.0 (Ph), 140.0, 139.6 (C=), 136.0, 135.8, 129.5, 129.4, 129.3, 128.4, 128.3, 128.2, 126.0 (Ph), 115.3, 115.1 (CH_2=), 63.4, 63.1 (C–N), 55.3 (CH_3O), 52.2, 52.0 (C–S), 21.2 (CH_3); IR ν_{max}: 2930.6, 2362.6, 1753.9, 1681.9, 1511.7, 1325.1, 1256.2, 1176.1, 700.5 cm^{-1}.
18. *(S)-N-(2-Methyl-1-phenylallyl)-2-oxo-2-phenylacetamide* (**3a**). White solid,^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, dd, J = 8.6, 1.2 Hz, NH), 7.64–7.32 (10H, m, Ph), 5.53 (1H, d, J = 8.8 Hz, CH–N), 5.07 (2H, s, CH_2=), 1.72 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.4 (C=O), 160.5 (C=O), 143.1 (C=), 138.8, 134.5, 131.3, 128.9, 128.5, 128.4, 128.0, 127.4 (Ph), 112.2 (CH_2=), 58.5 (C–N), 20.3 (CH_3); IR ν_{max}: 3286.6, 1683.2, 1660.5, 1632.1, 1579.4, 1543.3, 1218.5, 1173.3, 699.6, 667.3 cm^{-1}; EI-HRMS: calculated for $C_{18}H_{17}NO_2$, 279.1259; found, 279.1250.
19. *(S)-N-(3-Methyl-1-phenylbut-3-en-2-yl)-2-oxo-2-phenyl acetamide* (**3b**). White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, dd, J = 8.6, 1.6 Hz, NH), 7.60–7.10 (10H, m, Ph), 4.92 (1H, s, CH), 4.91 (1H, s, CH), 4.73 (1H, ddd, J = 8.6, 8.4, 6.0 Hz, CH–N), 3.06 (1H, dd, J = 14.0, 6.0 Hz, CH_aH_b), 2.90 (1H, dd, J = 14.0, 8.4 Hz, CH_bH_a), 1.84 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7 (C=O), 161.0 (C=O), 143.3 (C=), 137.1, 134.3, 133.1, 131.1, 129.1, 128.4, 128.3, 126.6 (Ph), 112.5 (CH_2=), 55.4 (C–N), 39.4 (CH_2), 19.8 (CH_3); IR ν_{max}: 3268.4, 2922.6, 1664.4, 1646.2, 1449.1, 1217.1, 898.6, 745.5, 697.4 cm^{-1}; FAB-HRMS: calculated for $C_{19}H_{20}NO_2$, 294.1494; found, 294.1563.

20. *(S)-N-(2,4-Dimethylpent-1-en-3-yl)-2-oxo-2-phenylacetamide* (**3c**). White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, dd, J = 8.4, 1.2 Hz, NH), 7.64–7.45 (5H, m, Ph), 4.94 (2H, s, CH_2=), 4.23 (1H, dd, J = 9.2, 7.6 Hz, CH–N), 1.98 (1H, m, CH), 1.76 (3H, s, CH_3), 0.96 (3H, d, J = 6.8 Hz, CH_3), 0.94 (3H, d, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.8 (C=O), 161.2 (C=O), 142.9 (C=), 134.5, 133.3, 131.2, 128.4 (Ph), 113.0 (CH_2=), 60.4 (CN), 29.6 (CH_3), 19.9 (CH_3), 19.2 (CH), 17.8 (CH_3); IR ν_{max}: 3269.4, 2964.8, 2952.2, 1685.8, 1663.1, 1630.7, 1555.6, 1450.3, 1220.6, 892.4, 704.9, 664.6 cm^{-1}; EI-HRMS: calculated for $C_{15}H_{19}NO_2$, 245.1416; found, 245.1406.

21. *(S)-N-(2-Methyl-1-phenylallyl)-2-oxo-2-p-methoxi-phenil-acetamide* (**3d**). Liquid,^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, J = 8.8 Hz, NH), 7.54–7.26 (7H, m, Ph), 7.00 (2H, d, J = 9.28 Hz, Ph), 5.51 (1H, d, J = 8.8 Hz, CH–N), 5.07 (2H, s, CH_2=), 3.88 (3H, s, OCH_3), 1.72 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.3 (C=O), 164.7 (C=O), 161.1 (Ph), 143.2 (C=), 139.0, 134.0, 128.8, 128.0, 127.3, 126.3, 113.8 (Ph), 112.2 (CH_2=), 58.9 (C–N), 55.5 (OCH_3), 20.2 (CH_3); IR ν_{max}: 3321.3, 2917.7, 1681.5, 1647.6, 1598.1, 1511.1, 1259.7, 1164.4, 801.7, 700.0 cm^{-1}.