Simple synthesis of 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones by the alkaline hydrolysis of Biginelli compounds

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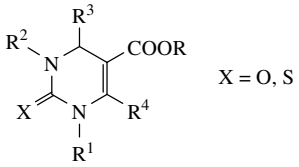
4-Aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones are final products of transformation of ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates in alkaline hydrolytic conditions.

The esters of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids (**1** X = O, R^3 = aryl) (so-called Biginelli compounds) are well known.[1,2] However, these compounds and their 2-thioxo analogues received significant attention only in the last two decades after their diverse biological activity was discovered. For example, they are active antihypertensive agents,[3,4] kinesin Eg5 inhibitors,[5] α_{1a} antagonists,[6] *etc*. Moreover, they were used in the syntheses of various heterocycles.[7,8]



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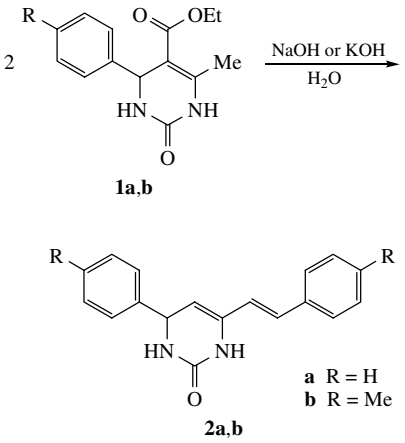
A principal feature of the reactivity of Biginelli compounds is their behaviour towards hydrolysis. However, the currently available data are limited and contradictory. As early as 1893, Pietro Biginelli showed[2] that the boiling of ethyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a** X = O, R = Et, $R^1 = R^2 = H$, R^3 = Ph, R^4 = Me) in water in the presence of KOH led to a deep decomposition of **1a** to result in benzaldehyde, ammonia, potassium carbonate, *etc*. Zigeuner[9] demonstrated that $N_{(1)}$-unsubstituted Biginelli compounds (**1** R = Et, CH_2Ph) were inactive under alkaline hydrolysis conditions (5% alcoholic solution of KOH, reflux), whereas $N_{(1)}$-methyl substituted ones underwent easy hydrolysis to form the corresponding tetrahydropyrimidine-5-carboxylic acids. In a review[7] devoted to Biginelli compounds, rather poor reactivity of their ester group towards hydrolysis was pointed out. This effect was attributed to the strong conjugation of this group with the adjacent C=C double bond. However, it was reported[10] that $N_{(1)}$-unsubstituted Biginelli compounds (**1** R = Me), when refluxed in methanol in the presence of an aqueous 1 M NaOH solution, were subjected to hydrolysis and decarboxylation to produce mixtures of 5-unsubstituted 4-hydroxyhexahydro-, 1,2,3,4-tetrahydro- and 1,2,5,6-tetrahydropyrimidin-2-ones.

Thus, it is interesting to study in detail the behaviour of Biginelli compounds under hydrolytic conditions. In this work, we report on the alkaline hydrolysis of Biginelli compounds using ethyl 6-methyl-4-phenyl- and 6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a**,**b** as examples.[11]

We found that, on refluxing **1a** in water in the presence of 3 equiv. of NaOH, gas evolution occurs in the initial period of time to result in abundant foam formation. Deep decomposition of **1a** with ring cleavage takes place under the reaction conditions. As the reaction proceeds, the water-insoluble white precipitate becomes yellowish and loose. According to TLC data, the precipitate taken at different points in time is a mixture of starting **1a** and at least four other compounds. With time, ratio of all components of the mixture changes and the most chromatographically mobile compound accumulates. In 5–6 h, this material becomes practically single. After completion of the reaction, the pale yellow solid was isolated by filtration and identified as 4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-one **2a** (Scheme 1). The yield of **2a** was 74% based on 2 equiv. of **1a** (Method A).†



Scheme 1 (Method A)

Alkaline hydrolysis of **1b** (aqueous NaOH, reflux) takes place in much the same way as **1a**. However, full conversion of **1b** into pyrimidine **2b** requires more time (about 9 h). Under these conditions, **2b** was obtained in 67% yield in practically pure form (Method A).†

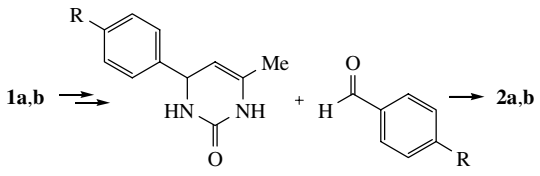
The application of potassium hydroxide instead of sodium hydroxide is less effective for the synthesis of **2a**,**b** from **1a**,**b**. Indeed, the heating of **1a** in a refluxed aqueous KOH (3 equiv.) solution for 6 h gives pure **2a** in 46% yield. Under the same conditions, transformation of **1b** into **2b** is not completed and

† *Synthesis of* **2a** *according to Method A*: a 100 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was charged with NaOH (0.632 g, 15.80 mmol), **1a** (1.328 g, 5.10 mmol) and water (25 ml). The resulting mixture was stirred and refluxed for 5 h 40 min. Within the first 1–1.5 h, abundant foaming takes place to result in removal of the insoluble material in part from the reaction area. For this reason, from time to time, the contents of the flask were shaken gently by hand. After the reaction was completed, the mixture containing a loose yellowish precipitate was cooled to room temperature; the solid was filtered off, washed with cold water and light petroleum and dried to give **2a** (0.519 g, 73.6%).

Similarly, the refluxing of **1b** (1.528 g, 5.57 mmol) and NaOH (0.668 g, 16.70 mmol) in water (30 ml) for 9 h produced **2b** (0.565 g, 66.6%).

Synthesis of **2a** *according to Method B*: a 100 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was charged with NaOH (0.583 g, 14.58 mmol), **1a** (1.263 g, 4.85 mmol), benzaldehyde (0.522 g, 4.92 mmol) and water (25 ml). The resulting mixture was stirred and refluxed for 5 h 40 min. After the reaction was completed, the mixture containing a loose yellowish precipitate was cooled to room temperature; the solid was filtered off, washed with cold water and light petroleum and dried to give **2a** (1.065 g, 79.4%).

Similarly, the refluxing of **1b** (1.685 g, 6.14 mmol), NaOH (0.737 g, 18.43 mmol) and 4-methylbenzaldehyde (0.773 g, 6.43 mmol) in water (34 ml) for 9 h yielded 1.429 g of **2b** containing a small amount of aldehyde **4b**. To purify **2b**, the material was refluxed with 7 ml of heptane, filtered hot, washed with boiling heptane (3×7 ml) and dried to give **2b** (1.321 g, 70.7%).



a R = H
b R = Me

Scheme 2

the product isolated after 9 h is a mixture of **1b** and **2b** in a 25:75 molar ratio (^{1}H NMR data).

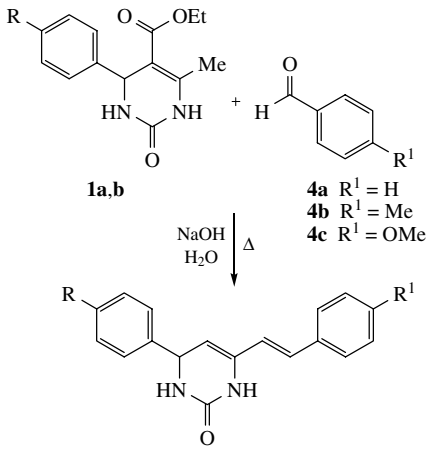
The formation of **2a**,**b** in the above reactions may be explained by the coupling of the corresponding 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-ones **3a**,**b** and aromatic aldehydes **4a**,**b**, which are produced as intermediates in the deep destruction of Biginelli compounds under the conditions applied (Scheme 2).‡

Surprisingly, though the process is obviously multistage, **2a**,**b** are formed in rather good yields (67–74%). It seems to depend on a number of various factors, in particular, on high hydrolytic stability of **2a**,**b** due to the presence of the conjugated aryldiene system in their molecules.

We supposed that the addition of corresponding aldehydes **4a**,**b** to the reactions of **1a**,**b** described above could trap intermediates **3a**,**b** to give hydrolytically stable **2a**,**b**. It would increase the degree of utilization of starting pyrimidines **1a**,**b** and the yields of **2a**,**b**. In fact, the refluxing of **1a** in water in the presence of NaOH (3 equiv.) and benzaldehyde **4a** (1 equiv.) for 5 h 40 min provides **2a** in high yield (79% based on 1 equiv. of **1a**) (Scheme 3) (Method B).† Under the same conditions, the reaction of **1b** with 4-methylbenzaldehyde **4b** for 9 h leads to **2b** in 71% yield.†

This approach can also be used in the synthesis of 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones **2** including asymmetric ones (**2** R ≠ R^1). Thus, the reaction of **1a** with anisic aldehyde **4c** (1.5 equiv.) in the presence of NaOH (3 equiv.) in water (reflux, 7 h) gives **2c** in 79% yield, and the treatment of **1b** with benzaldehyde (1.5 equiv.) under similar conditions (NaOH, water, reflux, 9 h) results in **2d** in 81% yield.§

The structures of **2a**–**d** were determined by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.¶ Note that all of the compounds were stereohomogeneous with (*E*)-configuration of the styryl fragment.



2a R = R^1 = H
2b R = R^1 = Me
2c R = H, R^1 = OMe
2d R = Me, R^1 = H

Scheme 3 (Method B)

‡ It was shown previously[12,13] that reaction of 6-methyl-4-phenyl- and 4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidin-2-ones with aromatic aldehydes in ethanol in the presence of KOH gives the corresponding 4-styryl-1,2,3,4-tetrahydropyrimidin-2-ones.

In summary, we found that Biginelli compounds are highly reactive towards aqueous-alkali solutions on heating. The resulting products were 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones. We also developed a procedure for the convenient synthesis of these pyrimidines based on the reaction of Biginelli compounds with aromatic aldehydes in the presence of an alkali on heating in water.

§ *Synthesis of* **2c**: this compound was prepared as described for **2a** according to Method B by reaction of **1a** (1.407 g, 5.41 mmol) with anisic aldehyde (1.115 g, 8.19 mmol) and NaOH (0.648 g, 16.20 mmol) in water (50 ml) for 7 h. After washing out the impurity of aldehyde **4c** with boiling heptane, the yield of **2c** was 1.306 g (78.9%).

Synthesis of **2d**: this compound was prepared as described for **2a** according to Method B by reaction of **1b** (1.534 g, 5.59 mmol) with benzaldehyde (0.919 g, 8.66 mmol) and NaOH (0.671 g, 16.78 mmol) in water (31 ml) for 9 h. After washing out benzaldehyde impurity with boiling heptane, the yield of **2d** was 1.314 g (80.9%).

¶ The IR spectra were obtained on a Bruker Equinox 55/S Fourier spectrometer in KBr pellets (for **2a**) or Nujol (for **2b**–**d**). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer at 300.13 (^{1}H) and 75.476 (^{13}C) MHz as solutions in [$^2H_6$]DMSO.

*4-Phenyl-6-[(*E*)-2-phenylvinyl]-1,2,3,4-tetrahydropyrimidin-2-one* **2a**: pale yellow crystals, mp 202–203 °C (ethanol; decomp.) (lit.,[13] mp 218 °C). ^{1}H NMR, δ: 8.46 [s, 1H, N(1)–H], 7.21–7.47 [m, 11H, 4-Ph, Ph in CH=CH–Ph and N(3)–H], 7.10 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 6.63 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 5.11 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz, $J_{\text{NH},4\text{-H}}$ 2.0 Hz), 5.07 (br. d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz). ^{13}C NMR, δ: 153.26 [C(2)], 145.03 [C(1) in 4-Ph], 136.58 [C(1) in CH=CH–*Ph*], 133.69 [C(6)], 128.72 [C(3) and C(5) in CH=CH–*Ph*], 128.58 [C(3) and C(5) in 4-Ph], 127.78 (CH=*C*H–Ph), 127.52 [C(4) in CH=CH–*Ph*], 127.26 [C(4) in 4-Ph], 126.39 [C(2) and C(6) in CH=CH–*Ph*], 126.20 [C(2) and C(6) in 4-Ph], 122.31 (*C*H=CH–Ph), 104.15 [C(5)], 55.11 [C(4)]. IR, ν/cm^{-1}: 3409, 3229, 3114 (ν_{NH}), 3081, 3056, 3025 [$\nu_{C(sp^2)–H}$], 1685 ($\nu_{C=O}$), 1659 ($\nu_{C=C}$), 1598, 1495 ($\nu_{CC\text{ in Ph}}$), 970 ($\delta_{C–H\text{ in }trans\text{-CH=CH}}$), 769, 752, 703, 689 ($\delta_{C_{arom}–H}$). Found (%): C, 78.03; H, 5.98; N, 10.09. Calc. for $C_{18}H_{16}N_2O$ (%): C, 78.24; H, 5.84; N, 10.14.

*4-(4-Methylphenyl)-6-[(*E*)-2-(4-methylphenyl)vinyl]-1,2,3,4-tetrahydropyrimidin-2-one* **2b**: pale yellow crystals, mp 184–185.5 °C (ethanol; decomp.). ^{1}H NMR, δ: 8.41 [s, 1H, N(1)–H], 7.33 [m, 2H, AA′ part of AA′XX′ spin system, C(2)H and C(6)H in CH=CH–C_6H_4Me, J_{ortho} 8.1 Hz], ~7.21 [1H, N(3)–H, the signals overlapped with signals of C_6H_4 protons], 7.19 [m, 2H, AA′ part of AA′BB′ spin system, C(2)H and C(6)H in 4-C_6H_4Me, J_{ortho} ~ 8.1 Hz], 7.17 [m, 2H, BB′ part of AA′BB′ spin system, C(3)H and C(5)H in 4-C_6H_4Me, J_{ortho} ~ 8.1 Hz], 7.15 [m, 2H, XX′ part of AA′XX′ spin system, C(3)H and C(5)H in CH=CH–C_6H_4Me, J_{ortho} 8.1 Hz], 7.05 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 6.56 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 5.05 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz, $J_{\text{NH},4\text{-H}}$ 2.0 Hz), 5.00 (br. d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz), 2.28 (s, 6H, 4-C_6H_4*Me*, CH=CH–C_6H_4*Me*). ^{13}C NMR, δ: 153.23 [C(2)], 142.10 [C(1) in 4-C_6H_4Me], 137.13 [C(4) in CH=CH–C_6H_4Me], 136.32 [C(4) in 4-C_6H_4Me], 133.79 [C(1) in CH=CH–C_6H_4Me], 133.65 [C(6)], 129.26 [C(3) and C(5) in 4-C_6H_4Me], 129.00 [C(3) and C(5) in CH=CH-C_6H_4Me], 127.34 (CH=*C*H–C_6H_4Me), 126.29 [C(2) and C(6) in CH=CH–C_6H_4Me], 126.12 [C(2) and C(6) in 4-C_6H_4Me], 121.31 (*C*H=CH–C_6H_4Me), 103.70 [C(5)], 54.80 [C(4)], 20.77 (CH=CHC_6H_4*Me*), 20.61 (4-C_6H_4*Me*). IR, ν/cm^{-1}: 3209, 3084 (ν_{NH}), 1683 ($\nu_{C=O}$), 1657 ($\nu_{C=C}$), 1507 ($\nu_{CC\text{ in }C_6H_4}$), 966 ($\delta_{C–H\text{ in }trans\text{-CH=CH}}$), 805 ($\delta_{C_{arom}–H}$). Found (%): C, 78.88; H, 6.53; N, 9.32. Calc. for $C_{20}H_{20}N_2O$ (%): C, 78.92; H, 6.62; N, 9.20.

*6-[(*E*)-2-(4-Methoxyphenyl)vinyl]-4-phenyl-1,2,3,4-tetrahydropyrimidin-2-one* **2c**: light yellow crystals, mp 207–208.5 °C (ethanol; decomp.). ^{1}H NMR, δ: 8.35 [s, 1H, N(1)–H], 7.24–7.40 [m, 7H, 4-Ph, C(2)H and C(6)H in C_6H_4OMe], 7.21 [br. d, 1H, N(3)–H, $J_{NH,4\text{-H}}$ 2.0 Hz], 7.03 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 6.91 [m, 2H, AA′ part of AA′XX′ spin system, C(3)H and C(5)H in C_6H_4OMe, J_{ortho} 8.7 Hz], 6.47 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 5.09 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz, $J_{NH,4\text{-H}}$ 2.0 Hz), 4.99 (br. d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.5 Hz), 3.75 (s, 3H, OMe). ^{13}C NMR, δ: 159.03 [C(4) in C_6H_4OMe], 153.19 [C(2)], 145.09 [C(1) in Ph], 133.81 [C(6)], 129.15 [C(1) in C_6H_4OMe], 128.47 [C(3) and C(5) in Ph], 127.65 [C(2) and C(6) in C_6H_4OMe], 127.14 [CH=*C*H–C_6H_4OMe and C(4) in Ph], 126.12 [C(2) and C(6) in Ph], 120.01 (*C*H=CH–C_6H_4OMe), 114.16 [C(3) and C(5) in C_6H_4OMe], 102.81 [C(5)], 55.08 [C(4) and OMe]. IR, ν/cm^{-1}: 3407, 3194 (ν_{NH}), 3084 [$\nu_{C(sp^2)–H}$], 1683 ($\nu_{C=O}$), 1656 ($\nu_{C=C}$), 1600, 1568, 1509 ($\nu_{CC\text{ in Ph and }C_6H_4}$), 1248 ($\nu_{as\ C–O–C}$), 1025 ($\nu_{s\ C–O–C}$), 968 ($\delta_{C–H\text{ in }trans\text{-CH=CH}}$), 826 ($\delta_{C_{arom}–H\text{ in }C_6H_4}$), 750, 701 ($\delta_{C_{arom}–H\text{ in Ph}}$). Found (%): C, 74.41; H, 5.92; N, 9.20. Calc. for $C_{19}H_{18}N_2O_2$ (%): C, 74.49; H, 5.92; N, 9.14.

References

1 P. Biginelli, *Ber.*, 1891, **24**, 1317.
2 P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360.
3 K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.
4 G. J. Grover, S. Dzwonczyk, D. M. McMullen, D. E. Normandin, C. S. Parham, P. G. Sleph and S. Moreland, *J. Cardiovasc. Pharmacol.*, 1995, **26**, 289.
5 S. J. Haggarty, T. U. Mayer, D. T. Miyamoto, R. Fathi, R. W. King, T. J. Mitchison and S. L. Schreiber, *Chem. Biol.*, 2000, **7**, 275.
6 D. Nagarathnam, S. W. Miao, B. Lagu, G. Chiu, J. Fang, T. G. M. Dhar, J. Zhang, S. Tyagarajan, M. R. Marzabadi, F. Q. Zhang, W. C. Wong, W. Y. Sun, D. Tian, J. M. Wetzel, C. Forray, R. S. L. Chang, T. P. Broten, R. W. Ransom, T. W. Schorn, T. B. Chen, S. O'Malley, P. Kling, K. Schneck, R. Benedesky, C. M. Harrell, K. P. Vyas and C. Gluchowski, *J. Med. Chem.*, 1999, **42**, 4764.
7 C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937.
8 C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879.
9 G. Zigeuner, C. Knopp and H. Blaschke, *Monatsh. Chem.*, 1976, **107**, 587.
10 T. G. Steele, C. A. Coburn, M. A. Patane and M. G. Bock, *Tetrahedron Lett.*, 1998, **39**, 9315.
11 K. Folkers, H. J. Harwood and T. B. Johnson, *J. Am. Chem. Soc.*, 1932, **54**, 3751.
12 G. Zigeuner, E. Fuchs and W. Galatik, *Monatsh. Chem.*, 1966, **97**, 43.
13 G. Zigeuner, H. Brunetti, E. Ziegler and M. Bayer, *Monatsh. Chem.*, 1970, **101**, 1767.

*4-(4-Methylphenyl)-6-[(*E*)-2-phenylvinyl]-1,2,3,4-tetrahydropyrimidin-2-one* **2d**: pale yellow crystals, mp 191–192 °C (ethanol; decomp.). ^{1}H NMR, δ: 8.41 [s, 1H, N(1)–H], 7.22–7.47 (m, 5H, Ph), 7.20 [m, 2H, AA′ part of AA′BB′ spin system, C(2)H and C(6)H in 4-MeC_6H_4, J_{ortho} 8.1 Hz], ~7.19 [1H, N(3)–H, the signals overlapped with signals of C_6H_4 protons], 7.17 [m, 2H, BB′ part of AA′BB′ spin system, C(3)H and C(5)H in 4-MeC_6H_4, J_{ortho} 8.1 Hz], 7.09 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 6.62 (d, 1H, CH in CH=CH, *J* 16.6 Hz), 5.07 (dd, 1H, 4-H, $J_{4\text{-H,5-H}}$ 4.5 Hz, $J_{NH,4\text{-H}}$ 2.0 Hz), 5.04 (br. d, 1H, 5-H, $J_{4\text{-H,5-H}}$ 4.5 Hz), 2.28 (s, 3H, Me). ^{13}C NMR, δ: 153.13 [C(2)], 141.97 [C(1) in C_6H_4Me], 136.53 [C(1) in Ph], 136.27 [C(4) in C_6H_4Me], 133.57 [C(6)], 128.94 [C(3) and C(5) in C_6H_4Me], 128.59 [C(3) and C(5) in Ph], 127.63 (CH=*C*H–Ph), 127.40 [C(4) in Ph], 126.28 [C(2) and C(6) in Ph], 126.05 [C(2) and C(6) in C_6H_4Me], 122.25 (*C*H=CH–Ph), 104.07 [C(5)], 54.76 [C(4)], 20.54 (Me). IR, ν/cm^{-1}: 3436, 3244, 3127 (ν_{NH}), 3077, 3020 [$\nu_{C(sp^2)–H}$], 1676 ($\nu_{C=O}$), 1656 ($\nu_{C=C}$), 1597, 1509 ($\nu_{CC\text{ in Ph and }C_6H_4}$), 965 ($\delta_{C–H\text{ in }trans\text{-CH=CH}}$), 806 ($\delta_{C_{arom}–H\text{ in }C_6H_4}$), 756, 693 ($\delta_{C_{arom}–H\text{ in Ph}}$). Found (%): C, 78.30; H, 6.27; N, 9.56. Calc. for $C_{19}H_{18}N_2O$ (%): C, 78.59; H, 6.25; N, 9.65.

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