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Substituent effects in ring-chain tautomerism of the condensation products of non-racemic 1,2-aminoalcohols with aromatic aldehydes

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ABSTRACT

The condensation of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes in methanol or water led to crystalline products, which proved to exist in $CDCl_3$ at 300 K as three-component (ring^{cis}-open-ring^{trans}) tautomeric mixtures. The electronic effects of the 2-aryl substituents on the tautomeric equilibria were described by the Hammett equation. Good correlations were found between the equilibrium constants and the Hammett–Brown parameter (σ^+) of the substituent X on the 2-phenyl group.

1. Introduction

The synthesis and derivatization of 1,2- and 1,3-aminoalcohols are of both pharmaceutical and chemical interest. These difunctional moieties are frequently occurring structural motifs in biologically active compounds. Non-racemic 1,2- and 1,3-aminoalcohols are often utilized as resolving agents in the preparation of enantiopure substances or as chiral auxiliaries in various asymmetric transformations.[1]

Oxazolidine derivatives, obtained by the condensation of 1,2-aminoalcohols with oxo compounds, are also widely applied as intermediates or catalysts in asymmetric syntheses.[2] Excellent enantioselectivities have been achieved in the alkynylation of aldehydes,[3] in the Diels–Alder reactions of 1,2-dihydropyridines[4] and in a domino Michael–aldol reaction[5] through the use of chiral oxazolidine organocatalysts. Also, high yields and enantiomeric excesses have been attained in the bisoxazolidine-catalyzed nitroaldol reactions of different aliphatic and aromatic aldehydes.[6]

The structures of N-unsubstituted oxazolidines can be characterized by tautomeric equilibria of the cyclic and the corresponding Schiff base open-chain forms. Although Baldwin's rules suggest that ring closure of the open form is an unfavored 5-*endo-trig* process, a rapid equilibrium reaction has been observed to occur in solution.[7,8]

The ring-chain tautomeric character of oxazolidine derivatives provides these compounds with dual reactivity (substitution at the NH and/or addition at the C=N group), which is widely utilized in various synthetic transformations, for example the Reformatsky[9] and Ugi reactions[10] with the participation of the open tautomeric forms, or N-acetylation of the cyclic forms via iminium intermediates.[11]

The diastereoselective formation of bicyclic lactams in the domino ring-closure reactions of chiral phenylglycinols with γ-, δ- or ε-keto acids was earlier rationalized in terms of the differences in the rates of the acylation steps for the ring-chain tautomeric oxazolidine intermediates. These lactams are valuable building blocks in the enantioselective synthesis of structurally diverse piperidine-containing natural products and bioactive molecules.[12] Thanks to their ring-chain tautomeric character, oxazolidines have been applied as aldehyde sources in carbon-transfer reactions toward fused pyran and pyridine derivatives[13] and in the modified Pictet–Spengler synthesis of tetrahydro-β-carbolines.[14] Reductive aminations of oxo compounds with 1,2-aminoalcohols occur via oxazolidine intermediates,[15] and the ring-chain tautomeric character of oxazolidines also contributes to the development of prodrugs[16] or the creation of dynamic combinatorial libraries.[17]

As concerns the analogous N-unsubstituted 1,3-X,N-heterocycles (X = O, S, NR), the substituent dependence of the ring-chain tautomeric equilibria of oxazolidines was thoroughly studied earlier.[7,8,18,19] Investigations of a considerable number of 2-aryl-substituted derivatives led to the conclusion that the tautomeric ratios were substantially influenced by the electronic properties of the aryl substituents. For the tautomeric equilibria of 2-(X-phenyl)-substituted oxazolidines, a linear Hammett-type correlation was found between the log$K$ (K = [ring]/[chain]) values of the equilibria and the Hammett–Brown electronic parameter (σ^+) of substituent X on the 2-phenyl group (Eq. 1):[7,8,18,19]

$$\log K = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

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In contrast with these earlier reports on ring-chain tautomerism, unusual results were presented in a recent paper.[20] Benzylideneamino derivatives were synthesized through the condensations of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes, these reactions reportedly furnishing two-component ring-chain tautomeric mixtures.

Rather surprisingly, the amount of the Schiff base form in the tautomeric mixtures of the products formed in the reactions of (*S*)-2-amino-2-phenylethanol with substituted benzaldehydes varied from 92% to 99%. Interestingly, significant differences were not observed in the amounts of the open-chain form in the tautomeric mixtures of products formed in the reactions of (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes. For example, the amounts of (*S*)-2-(4-nitrobenzylideneamino)-3-phenylpropanol and (*S*)-2-(4-dimethylamino-benzylideneamino)-3-phenylpropanol in the tautomeric mixtures were 90% and 87%, respectively. Furthermore, for the ring-closed tautomer formed in the tautomeric mixture, a distinction of two epimers was not reported.[20]

In order to clarify this situation, we have re-examined the data presented in the paper of Wu et al.[20] We prepared the same (*S*)-2-benzylideneamino-2-phenylethanols and (*S*)-2-benzylideneamino-3-phenylpropanols and also additional model compounds.

2. Results and discussion

Harsh reaction conditions (e.g. long reflux times in high-boiling-point solvents, with the application of water traps or dehydrating agents) have at times been applied for the condensation of amino alcohols with aldehydes.[21] Wu et al. reacted (*S*)-2-amino-2-phenylethanol **1** or (*S*)-2-amino-3-phenylpropanol **2** with equivalent amounts of different benzaldehydes in anhydrous THF in the presence of $MgSO_4$ for 1 h.[20]

We earlier reported that 1,2- and 1,3-aminoalcohols react conveniently with aromatic aldehydes without any additive to yield the condensation products quantitatively within a few hours in MeOH or EtOH even at room temperature.[18,19] In the present study we followed this synthetic procedure. Moreover, in view of the emerging importance of water as a versatile solvent in organic synthesis,[22] including various condensations (e.g. the Ugi four-center three-component reaction,[23] or cyclocondensations of β-aminocarboxamides and various ketones[24]), the reactions of aminoalcohols **1** and **2** with aromatic aldehydes were also attempted in aqueous medium.

When **1** or **2** was reacted with an equivalent amount of the corresponding aldehyde in absolute MeOH, and the mixture was left to stand at room temperature for 1 h, condensations took place nearly quantitatively. After evaporation of the solution, each compound **3a–i**, **4a–i** was obtained as a stable crystalline product (Scheme 1). When the condensations of aminoalcohol **1** or **2** with the equivalent amounts of aldehydes were performed in distilled water, the mixtures were stirred vigorously at room temperature for 1 h and the precipitated products **3a–i**, **4a–i** were collected by filtration. The yields for the aqueous reactions proved to be somewhat higher than those for the condensations in MeOH.

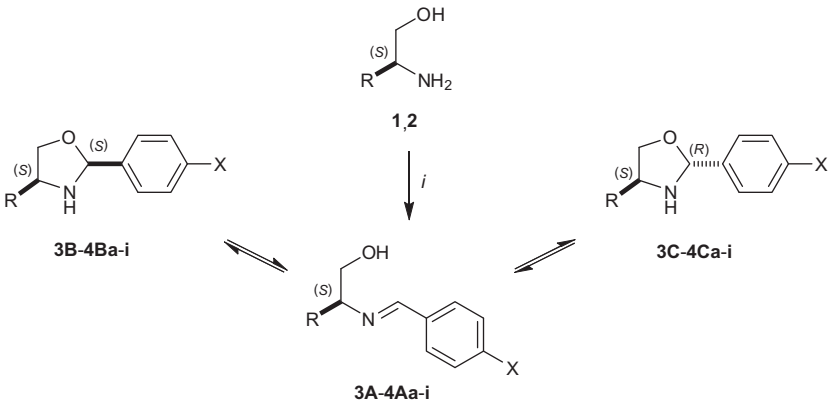
Since the compounds synthesized in MeOH and in H_2O are necessarily identical, we studied the tautomerism only on the compounds synthesized in MeOH. We found that in $CDCl_3$ solution at 300 K compounds **3** and **4** participated in three-component ring-chain tautomeric equilibria involving C-2 epimeric cyclic forms (**B** and **C**) besides the open tautomer (**A**) (Scheme 1). Since the NMR spectroscopic characterizations were very similar for **3a–i** and **4a–i**, only the data on **3a** and **4a** were chosen to illustrate the ^{1}H NMR spectra of the tautomeric compounds prepared and the relative configurations of the major and minor ring-closed tautomers (see Section 4). The NOE interaction observed between H-2 and H-4 in the NOESY spectra indicated that the major ring form had the *cis* configuration **B**. 2,4-Diaryl substituents did not change the sequence of the chemical shifts of the characteristic O–C*H*Ar–N and N=C*H*Ar protons.

In contrast with the three-component tautomeric equilibria detected in our work, Wu et al. reported only two components **A** and **B** in the tautomeric mixtures of the oxazolidines prepared. They did not describe the minor *trans* C-2 epimeric form **C**.[20]

Figures 1 and 2 show the 500 MHz ^{1}H NMR spectra of the products **3a**, and **4a** of the reactions of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with *p*-nitrobenzaldehyde. In Figure 1, the singlets at 5.70 and 5.83 ppm are those of H-2 in the two ring-closed tautomers, while the azomethine singlet is at 8.48 ppm. In Figure 2, the corresponding singlets are shifted to lower values, with the H-2 singlets of the ring-closed tautomers at 5.55 and 5.70 ppm and the azomethine singlet at 8.02 ppm. Both spectra also contain the corresponding triplets or multiplets of H-4 of the epimeric ring forms of **3a** and **4a**.

In Figure 1, the well-separated triplets at 4.37 and 4.43 ppm correspond to H-4 in the major and minor ring forms of **3a**. In **4a**, multiplets appear at 3.73–3.81 ppm for H-4 of the major epimeric ring form, and overlapping multiplets are observed at 3.81–3.90 ppm for H-4 in the minor epimer (Fig. 2). The amounts of the tautomeric forms are also indicated in the spectra. Of the C-2 epimers, the major ring form in the tautomeric equilibria of **3a** and **4a** contains H-2 and H-4 in the *cis* position **B** (Tables 1 and 2).

The reported contents of the tautomeric forms in the tautomeric equilibria in the two studies differ drastically.[19] For instance, Wu



R = Ph: **1**, **3**; R= CH_2 Ph: **2**, **4**; X = **a**, NO_2; **b**, CN; **c**, Br; **d**, Cl; **e**, H; **f**, F; **g**, He; **h**, OMe; **i**, HMe_2.

Scheme 1. Reagents, conditions and yields: (i) XC_6H_4CHO, MeOH or H_2O, rt, 1 h, 61–99%.

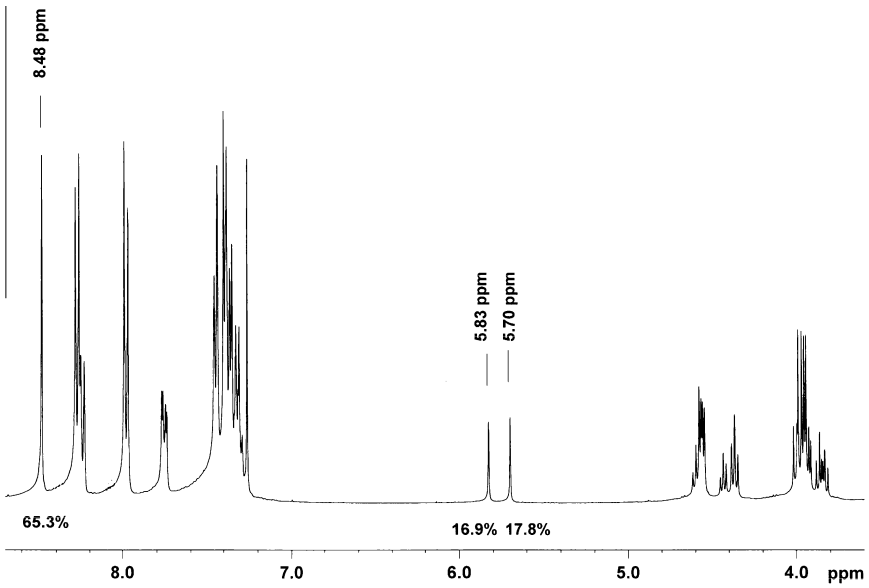


Figure 1. Part of the ^{1}H NMR spectrum of **3a**. Chemical shifts of the characteristic N=C*H* and N–C*H*–O protons in the three tautomeric forms are indicated, together with the amounts determined for the three tautomers. The spectrum was recorded after the solution in $CDCl_3$ had been allowed to stand at 300 K for 1 day.

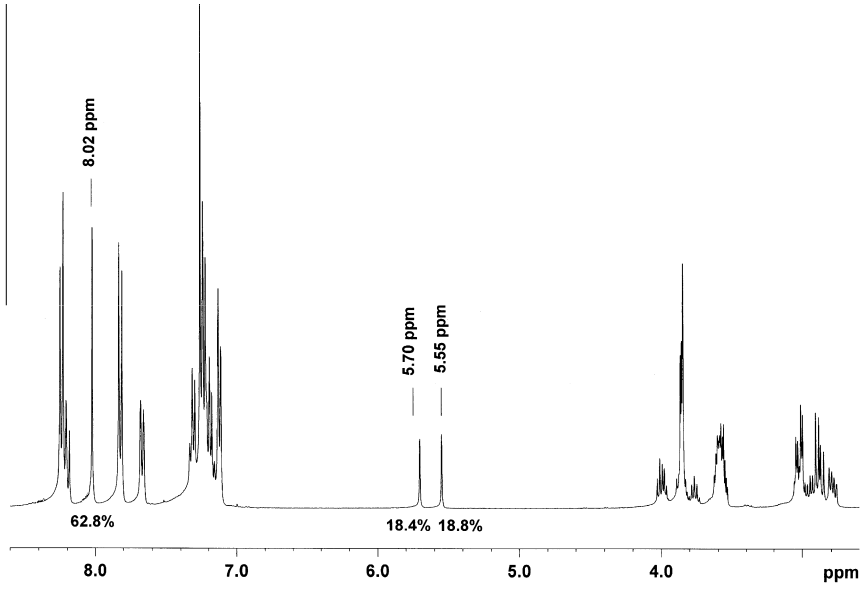


Figure 2. Part of the ^{1}H NMR spectrum of **4a**. Chemical shifts of the characteristic N=C*H* and N–C*H*–O protons in the three tautomeric forms are indicated, together with the amounts determined for the three tautomers. The spectrum was recorded after the solution in $CDCl_3$ had been allowed to stand at 300 K for 1 day.

et al. gave the measured amount of the open-chain form for *p*-NO_2-substituted compound **3a** as 92%, whereas in the present work it was only 65.3%. Wu et al. detected the Schiff base form in almost identical amounts in the ring-chain tautomeric mixtures of the various condensation products. As an example, for compound **4a** with a *p*-NO_2 group and compound **4h** with a *p*-OMe substituent, the amounts of open-chain form detected were 90% and 87%, respectively. The measured values did not indicate any correlation between the open-chain form (or cyclic form) and the different electronic characters of groups X.

To study the 2-aryl substituent dependence of $\log K_B$ and $\log K_C$ ($K_B = [\mathbf{B}]/[\mathbf{C}]$, $K_C = [\mathbf{C}]/[\mathbf{A}]$), we applied Eq. 1 to the data on compounds **3** and **4**. Good linear correlations were obtained between the $\log K_B$ and $\log K_C$ values and the Hammett–Brown parameter σ^+ of substituent X on the 2-phenyl group, for both the $\mathbf{B} \rightleftharpoons \mathbf{A}$ and the $\mathbf{C} \rightleftharpoons \mathbf{A}$ equilibria (Fig. 3 and Table 3).

3. Conclusion

Our results demonstrate that, in contrast with the recently reported data,[20] the condensation products of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes exist in $CDCl_3$ at 300 K as three-component tautomeric mixtures containing not only the open tautomeric form, but also C-2 epimeric oxazolidines as minor components. Careful analysis of the influence of the electronic character of the aryl substituents at position 2 on the ring-chain tautomeric equilibria revealed that it could be described by the Hammett equation.

Table 1
Amounts (%) of tautomeric forms **A**, **B,** and **C** in tautomeric equilibria for compounds **3** ($CDCl_3$, 300 K) determined in the present study, and amounts (%) of Schiff base form **A** in the tautomeric mixture for compounds **3a**, **3d**, **3e**, **3g** and **3h** ($CDCl_3$) reported in a previous study[20]

Compound	X	σ^+	A (%)	B (%)	C (%)	A[a] (%)
3a	*p*-NO_2	0.79	65.3	17.8	16.9	92
3b	*p*-CN	0.659	67.6	16.8	15.6	—
3c	*p*-Br	0.15	79.7	11.0	9.3	—
3d	*p*-Cl	0.114	81.1	10.5	8.4	98
3e	H	0	83.5	9.2	7.3	99
3f	*p*-F	−0.07	85.1	8.4	6.5	—
3g	*p*-Me	−0.311	87.6	7.2	5.2	94
3h	*p*-OMe	−0.778	91.7	4.5	3.8	95
3i	*p*-NMe_2	−1.7	97.0	1.6	1.4	—

[a] Data from Ref. 20.

Table 2
Amounts (%) of tautomeric forms **A**, **B** and **C** in tautomeric equilibria for compounds **4** ($CDCl_3$, 300 K) determined in the present study, and amounts (%) of Schiff base form **A** in the tautomeric mixture for compounds **4a**, **4d**, **4e**, **4g,** and **4h** ($CDCl_3$) reported in a previous study[20]

Compound	X	σ^+	A (%)	B (%)	C (%)	A[a] (%)
4a	*p*-NO_2	0.79	62.8	18.8	18.4	90
4b	*p*-CN	0.659	65.6	17.9	16.5	—
4c	*p*-Br	0.15	79.5	11.6	8.9	—
4d	*p*-Cl	0.114	80.0	11.3	8.7	96
4e	H	0	82.5	9.9	7.6	98
4f	*p*-F	−0.07	84.3	9.0	6.7	—
4g	*p*-Me	−0.311	86.8	7.9	5.3	94
4h	*p*-OMe	−0.778	93.2	4.2	2.6	87
4i	*p*-NMe_2	−1.7	97.6	1.4	1.0	—

[a] Data from Ref. 20.

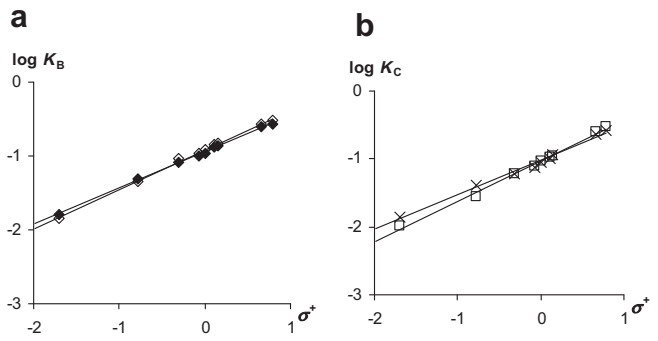


Figure 3. (a) Plots of log K_B ($CDCl_3$, 300 K) for **3B** (♦) and **4B** (◇) versus Hammett–Brown parameter σ^+. (b) Plots of log K_C ($CDCl_3$, 300 K) for **3C** (×) and **4C** (□) versus Hammett–Brown parameter σ^+.

Table 3
Linear regression analysis data on the tautomeric equilibria of compounds **3** and **4**

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] ($\log K_{X=H}$)	Correlation coefficient
3A ⇌ **3B**	9	0.49 (±0.01)	−0.94 (±0.01)	0.999
3A ⇌ **3C**	9	0.50 (±0.02)	−1.02 (±0.02)	0.994
4A ⇌ **4B**	9	0.54 (±0.01)	−0.92 (±0.01)	0.999
4A ⇌ **4C**	9	0.60 (±0.02)	−1.03 (±0.01)	0.997

[a] Standard error in parentheses.

4. Experimental

Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Merck Kieselgel 60 F_{254} plates were used for TLC. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at 300 K on a Bruker AVANCE DRX 500 spectrometer at 500.13 MHz. Chemical shifts are given in δ (ppm) relative to TMS as an internal standard; multiplicities were recorded as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet) or m (multiplet). For the equilibria in the tautomeric compounds to be established, the samples were dissolved in $CDCl_3$ and the solutions were allowed to stand at ambient temperature for 24 h before the ^{1}H NMR spectra were run.

(*S*)-2-Amino-2-phenylethanol **1** and (*S*)-2-amino-3-phenylpropanol **2** were purchased from Aldrich.

4.1. Reactions of (*S*)-2-amino-2-phenylethanol 1 or (*S*)-2-amino-3-phenylpropanol 2 with aromatic aldehydes

Method A: Aminoalcohol **1** or **2** (3 mmol) was dissolved in MeOH (20 mL) and an appropriate aromatic aldehyde (3 mmol) was added. After the mixture had stood for 1 h at room temperature, the solvent was evaporated off and the oily products were crystallized on treatment with diisopropyl ether or *n*-hexane. Yields: 61–99%.

Method B: A mixture of aminoalcohol **1** or **2** (3 mmol), distilled water (20 mL) and an equivalent amount of aromatic aldehyde (3 mmol) was stirred vigorously at room temperature for 1 h. The precipitated crystalline product was filtered off. Yields: 71–99%.

All compounds (**3a**–**3i** and **4a**–**4i**) gave satisfactory data on elemental analysis (C, H, N ±0.3%).

With regard to the similarities in the ^{1}H and ^{13}C NMR spectroscopic data for compounds **3a**–**3i** and compounds **4a**–**4i**, the full spectra of the *major* tautomers are described for only two representatives **3a** and **4a** of these sets of compounds. For the other cases, only the characteristic O–C*H*Ar–N and N=C*H*Ar protons are listed.

Compound **3a**: Yellow crystals. Yield: 0.66 g (82%, Method A), 0.81 g (99%, Method B), mp 74.5–76.5 °C (*i*Pr_2O). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.46; H, 5.21; N, 10.39.

Compound **3aA**: ^{1}H NMR: δ 8.48 (s, 1H, N=C*H*Ar), 8.28 (d, J = 8.7 Hz, 2H, $C_6H_4NO_2$), 7.98 (d, J = 8.7 Hz, 2H, $C_6H_4NO_2$), 7.75 (dd, J = 8.9, 2.9 Hz, 2H, C_6H_5), 7.44 (d, J = 7.5 Hz, 2H, C_6H_5), 7.39 (d, J = 7.0 Hz, 2H, C_6H_5), 4.56 (q, J = 4.7 Hz, 1H, NC*H*,), 4.05–3.90 (m, 2H, OCH_2), 1.81 (br s, 1H, O*H*) ppm. ^{13}C NMR: δ 160.8 (C-2), 149.7, 141.9, ($C_6H_4NO_2$), 129.8 ($C_6H_4NO_2$), 129.5, 128.6, 128.1 (C_6H_5), 124.6 ($C_6H_4NO_2$), 77.2 (C-4), 68.3 (C-5) ppm. Compound **3aB**: ^{1}H NMR: δ 5.70 (s, 1H, NC*H*O) ppm. Compound **3aC**: ^{1}H NMR: δ 5.83 (s, 1H, NC*H*O) ppm.

Compound **3b**: Yellow crystals. Yield: 0.60 g (79%, Method A), 0.61 g (81%, Method B), mp 70–72.5 °C. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.40; H, 5.63; N, 11.23. Compound **3bA**: ^{1}H NMR: δ 8.43 (s, 1H, N=C*H*Ar). Compound **3bB**: ^{1}H NMR: δ 5.65 (s, 1H, NC*H*O) ppm. Compound **3bC**: ^{1}H NMR: δ 5.78 (s, 1H, NC*H*O) ppm.

Compound **3c**: White crystals. Yield: 0.57 g (63%, Method A), 0.79 g (87%, Method B), mp 71–73 °C (*i*Pr_2O). Anal. Calcd for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60. Found: C, 58.96; H, 4.66; N, 4.63.

Compound **3cA**: ^{1}H NMR: δ 8.35 (s, 1H, N=C*H*Ar). Compound **3cB**: ^{1}H NMR: δ 5.56 (s, 1H, NC*H*O) ppm. Compound **3cC**: ^{1}H NMR: δ 5.66 (s, 1H, NC*H*O) ppm.

Compound **3d**: White crystals. Yield: 0.55 g (70%, Method A), 0.55 g (71%, Method B), mp 60–63 °C (*i*Pr_2O). Anal. Calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.19; H, 5.45; N, 5.37.

Compound **3dA**: ^{1}H NMR: δ 8.36 (s, 1H, N=C*H*Ar). Compound **3dB**: ^{1}H NMR: δ 5.58 (s, 1H, NC*H*O) ppm. Compound **3dC**: ^{1}H NMR: δ 5.67 (s, 1H, NC*H*O) ppm.

Compound **3e**: White crystals. Yield: 0.56 g (83%, Method A), 0.67 g (99%, Method B), mp 69–70 °C (lit.[25] mp 70–71 °C). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.29; H, 6.68; N, 6.24.

Compound **3eA**: ^{1}H NMR: δ 8.40 (s, 1H, N=C*H*Ar). Compound **3eB**: ^{1}H NMR: δ 5.61 (s, 1H, NC*H*O) ppm. Compound **3eC**: ^{1}H NMR: δ 5.67 (s, 1H, NC*H*O) ppm.

Compound **3f**: Yellow crystals. Yield: 0.64 g (88%, Method A), 0.61 g (84%, Method B), mp 63–65 °C (*n*-hexane). Anal. Calcd for $C_{15}H_{14}FNO$: C, 74.06; H, 5.80; N, 5.76. Found: C, 74.17; H, 5.83; N, 5.73.

Compound **3fA**: ^{1}H NMR: δ 8.37 (s, 1H, N=C*H*Ar). Compound **3fB**: ^{1}H NMR: δ 5.58 (s, 1H, NC*H*O) ppm. Compound **3fC**: ^{1}H NMR: δ 5.66 (s, 1H, NC*H*O) ppm.

Compound **3g**: White crystals. Yield: 0.65 g (90%, Method A), 0.68 g (94%, Method B), mp 75.5–76.5 °C (*i*Pr$_2$O). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.20; H, 7.19; N, 5.88.

Compound **3gA**: ^{1}H NMR: δ 8.37 (s, 1H, N=C*H*Ar). Compound **3gB**: ^{1}H NMR: δ 5.57 (s, 1H, NC*H*O) ppm. Compound **3gC**: ^{1}H NMR: δ 5.63 (s, 1H, NC*H*O) ppm.

Compound **3h**: White crystals. Yield: 0.74 g (92%, Method A), 0.75 g (96%, Method B), mp 88.5–89.5 °C. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.41; H, 6.69; N, 5.47.

Compound **3hA**: ^{1}H NMR: δ 8.34 (s, 1H, N=C*H*Ar). Compound **3hB**: ^{1}H NMR: δ 5.56 (s, 1H, NC*H*O) ppm. Compound **3hC**: ^{1}H NMR: δ 5.61 (s, 1H, NC*H*O) ppm.

Compound **3i**: White crystals. Yield: 0.64 g (80%, Method A), 0.73 g (91%, Method B), mp 65–65.5 °C (*i*Pr$_2$O). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.93; H, 7.48; N, 10.40.

Compound **3iA**: ^{1}H NMR: δ 8.24 (s, 1H, N=C*H*Ar). Compound **3iB**: ^{1}H NMR: δ 5.53 (s, 1H, NC*H*O) ppm. Compound **3iC**: ^{1}H NMR: δ 5.57 (s, 1H, NC*H*O) ppm.

Compound **4a**: Yellow crystals. Yield: 0.75 g (88%, Method A), 0.78 g (92%, Method B), mp 96–97.5 °C. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.81; H, 5.64; N, 9.82.

Compound **4aA**: ^{1}H NMR: δ 8.25 (d, J = 8.7 Hz, 2H, $C_6H_4NO_2$), 8.02 (s, 1H, N=C*H*Ar), 7.82 (d, J = 8.8 Hz, 2H, $C_6H_4NO_2$), 7.67 (dd, J = 8.8, 1.0 Hz, 1H, $CH_2C_6H_5$), 7.23 (d, J = 7.7 Hz, 2H, $CH_2C_6H_5$), 7.12 (d, J = 7.5 Hz, 2H, $CH_2C_6H_5$), 3.86 (t, J = 3.2 Hz, 2H, OCH_2), 3 67–3.52 (m, 1H, NC*H*), 3.02 (dd, J = 10.0, 5.3 Hz, 1H, $CH_2C_6H_5$), 2.88 (dd, J = 13.4, 8.5 Hz, 1H, $CH_2C_6H_5$), 1.78 (br s, 1H, O*H*) ppm. ^{13}C NMR: δ 160.5 (C-2), 149.6, 141.9 ($C_6H_4NO_2$), 138.8, 130.3 ($CH_2C_6H_5$), 129.5 ($C_6H_4NO_2$), 129.1, 127.1, ($CH_2C_6H_5$), 124.5 ($C_6H_4NO_2$), 74.9 (C-4), 66.5 (C-5), 39.5 ($CH_2C_6H_5$) ppm. Compound **4aB**: ^{1}H NMR: δ 5.55 (s, 1H, NC*H*O) ppm. Compound **4aC**: ^{1}H NMR: δ 5.70 (s, 1H, NC*H*O) ppm.

Compound **4b**: White crystals. Yield: 0.77 g (98%, Method A), 0.79 g (99%, Method B), mp 72.5–73.5 °C. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.44; H, 6.07; N, 10.64.

Compound **4bA**: ^{1}H NMR: δ 7.98 (s, 1H, N=C*H*Ar). Compound **4bB**: ^{1}H NMR: δ 5.50 (s, 1H, NC*H*O) ppm. Compound **4bC**: ^{1}H NMR: δ 5.66 (s, 1H, NC*H*O) ppm.

Compound **4c**: White crystals. Yield: 0.57 g (78%, Method A), 0.81 g (85%, Method B), mp 65–67 °C (*i*Pr$_2$O). Anal. Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.25; H, 5.09; N, 4.46.

Compound **4cA**: ^{1}H NMR: δ 7.92 (s, 1H, N=C*H*Ar). Compound **4cB**: ^{1}H NMR: δ 5.41 (s, 1H, NC*H*O) ppm. Compound **4cC**: ^{1}H NMR: δ 5.55 (s, 1H, NC*H*O) ppm.

Compound **4d**: White crystals. Yield: 0.73 g (89%, Method A), 0.76 g (92%, Method B), mp 73.5–74.5 °C. Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.35; H, 5.86; N, 5.10.

Compound **4dA**: ^{1}H NMR: δ 7.93 (s, 1H, N=C*H*Ar). Compound **4dB**: ^{1}H NMR: δ 5.42 (s, 1H, NC*H*O) ppm. Compound **4dC**: ^{1}H NMR: δ 5.56 (s, 1H, NC*H*O) ppm.

Compound **4e**: White crystals. Yield: 0.66 g (91%, Method A), 0.68 g (95%, Method B), mp 78.5–79.5 °C (lit.[26] mp 78–80 °C). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 79.92; H, 7.13; N, 5.87.

Compound **4eA**: ^{1}H NMR: δ 8.02 (s, 1H, N=C*H*Ar). Compound **4eB**: ^{1}H NMR: δ 5.46 (s, 1H, NC*H*O) ppm. Compound **4eC**: ^{1}H NMR: δ 5.58 (s, 1H, NC*H*O) ppm.

Compound **4f**: White crystals. Yield: 0.53 g (61%, Method A), 0.55 g (72%, Method B), mp 81.5–83 °C (*i*Pr$_2$O). Anal. Calcd for $C_{16}H_{16}FNO$: C, 74.69; H, 6.27; N, 5.44. Found: C, 74.41; H, 6.29; N, 5.41.

Compound **4fA**: ^{1}H NMR: δ 7.94 (s, 1H, N=C*H*Ar). Compound **4fB**: ^{1}H NMR: δ 5.43 (s, 1H, NC*H*O) ppm. Compound **4fC**: ^{1}H NMR: δ 5.56 (s, 1H, NC*H*O) ppm.

Compound **4g**: White crystals. Yield: 0.67 g (88%, Method A), 0.69 g (91%, Method B), mp 88.5–89.5 °C. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.45; H, 7.53; N, 5.50.

Compound **4gA**: ^{1}H NMR: δ 7.98 (s, 1H, N=C*H*Ar). Compound **4gB**: ^{1}H NMR: δ 5.42 (s, 1H, NC*H*O) ppm. Compound **4gC**: ^{1}H NMR: δ 5.54 (s, 1H, NC*H*O) ppm.

Compound **4h**: White crystals. Yield: 0.53 g (66%, Method A), 0.77 g (95%, Method B), mp 78–79 °C (*i*Pr$_2$O). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.98; H, 7.14; N, 5.22.

Compound **4hA**: ^{1}H NMR: δ 7.93 (s, 1H, N=C*H*Ar). Compound **4hB**: ^{1}H NMR: δ 5.41 (s, 1H, NC*H*O) ppm. Compound **4hC**: ^{1}H NMR: δ 5.52 (s, 1H, NC*H*O) ppm.

Compound **4i**: White crystals. Yield: 0.65 g (77%, Method A), 0.75 g (89%, Method B), mp 119.5–120.5 °C. Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.80; H, 7.89; N, 9.88.

Compound **4iA**: ^{1}H NMR: δ 7.87 (s, 1H, N=C*H*Ar). Compound **4iB**: ^{1}H NMR: δ 5.38 (s, 1H, NC*H*O) ppm. Compound **4iC**: ^{1}H NMR: δ 5.49 (s, 1H, NC*H*O) ppm.

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