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One-pot, three-component condensation of 2-hydroxybenzaldehyde derivatives, primary amines with alkyl isocyanides to N-alkyl-2-(2-hydroxyphenyl)-2-imino-acetamides

Research Article

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Abstract: One-pot, three-component condensation of 2-hydroxybenzaldehyde derivatives, primary amines with alkyl isocyanides is reported. N-alkyl-2-(2-hydroxyphenyl)-2-iminoacetamide derivatives are generated presumably *via* the preliminary formation of N, N'-disubstituted benzo[b]furan-2,3-diamines and subsequent oxidation with molecular oxygen.

Keywords: *Ugi reaction • Three-component • 2-Hydroxybenzaldehyde derivatives*

1. Introduction

Multicomponent reactions (MCRs) [1-5] in general and isocyanide-based multicomponent reactions (IMCRs) [6-10] in particular have attracted the attention of chemist's during the past years. These reactions are well defined and suited for combinational library synthesis due to the fact that products are formed in one-pot reactions [11-12]. The most popular IMCR is probably the Ugi reaction, in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl aminoamide containing four independently varying groups [13]. The Brönsted properties of carboxylic acids in Ugi MCR allow faster imine formation and addition of the moderately nucleophilic isocyanide to the activated iminiums. Subsequent trapping of the nitrilium intermediate by carboxylate followed by the irreversible acyl transfer step, known as the Mumm rearrangement [14], associated with the Ugi reaction seems to be responsible for the displacement of various equilibria. In a recently disclosed novel Ugi-type process, phenols have been used instead of carboxylic acids [15-20]. These reactions involve an irreversible Smiles rearrangement in place of the traditional Mumm acyl transfer. Utilization of electron deficient *o*- and *p*-phenols, salicylic derivatives and heteroaromatic phenols as the acidic surrogate in 4-CR leading to *N*-arylamides associated with Smiles rearrangement has been reported [20].

Utilization of bifunctional starting materials, in which the participating functional groups of two components of the 4CC reaction are present in one structure, is another strategy to increase scaffold diversity. The Reaction of bifunctional starting materials, such as 2-(2-formylphenoxy)acetic acid or levulinic acid containing either an aldehyde or a ketone and carboxylic acid functional groups in Ugi three-component condensation (3CC) reactions to lactam structures has been previously reported [21,22]. These results prompted us to explore the 3CC of primary amines, and isocyanides with a bifunctional starting material, containing aldehyde and hydroxy functional groups. Herein, we report the direct synthesis of novel *N*-alkyl-2-(2-hydroxyphenyl)-2-iminoacetamide derivatives *via* one-pot, three component condensation of 2-hydroxybenzaldehyde derivatives, primary aliphatic, aromatic or heteroaryl amines with alkyl isocyanides in acetonitrile.

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2. Experimental Procedure

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and were uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-500 AVANCE spectrometer. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

2.1. General procedure for the synthesis of 1a-q

Aniline (0.093 g, 1.0 mmol) and cyclohexyl isocyanide (0.109 mL, 1.0 mmol) were successively added to a solution of salicylaldehyde (0.122 g, 1.0 mmol) in acetonitrile (10 mL). The resulting solution was refluxed with stirring for 6 h. The solvent was then removed under reduced pressure and the residue was recrystalized from methanol to afford 1a-q.

2.1.1. N-cyclohexyl-2-(2-hydroxyphenyl)-2-(phenylimino)acetamide (1a).

Colorless crystal, mp.: 183-185^{0}C; ^1H NMR: δ = 0.84-1.65 (m, 10H), 3.80-3.82 (m, 1H), 5.45 (d, J = 8.0 Hz, 1H), 6.93-7.55 (m, 9H), 13.31 (s, 1H); ^{13}C NMR: δ = 24.8, 25.6, 32.8, 48.5, 116.7, 118.5, 119.4, 121.7, 126.5, 129.7, 131.1, 134.3, 149.6, 162.5, 168.5; IR (KBr): ν_{max} (cm^{-1}): 3320 (NH and OH), 1673 (C=O); MS (EI, 70 eV): m/z 322 (M$^+$, 2), 196 (84), 126 (45), 77 (100); C, H, N-analysis calcd. for $C_{20}H_{22}N_2O_2$; C, 74.51, H, 6.88, N, 8.69; found: C, 74.81; H, 6.39; N, 8.99.

2.1.2. N-tert-butyl-2-(2-hydroxyphenyl)-2-(phenylimino)acetamide (1b).

Brown crystal, mp.: 175-177^{0}C; ^1H NMR: δ = 1.14 (s, 9H), 5.19 (s, 1H), 6.91-7.69 (m, 9H), 13.27 (s, 1H); ^{13}C NMR: δ = 28.8, 53.0,118.6 ,119.5 ,121.9 ,122.5 ,126.4, 129.3 ,129.6 ,131.2, 134.3 ,146.8 ,162.5 ,168.5; IR (KBr): ν_{max} (cm^{-1}): 3321 (NH and OH), 1670 (C=O); MS (EI, 70 eV): m/z 296 (M$^+$, 2), 196 (46), 100 (65), 77 (60), 57(100); C, H, N-analysis calcd. for $C_{18}H_{20}N_2O_2$; C, 72.95; H, 6.80; N, 9.45; found: C,72.63; H, 7.02; N, 9.11.

2.1.3. N-cyclohexyl-2-(2-hydroxyphenyl)-2-(pyridin-2-ylimino)acetamide (1c).

Yellow crystal, mp.: 149-151^{0}C; ^1H NMR: δ = 1.21-1.88 (m, 10H), 3.00 (bs, 2H), 6.89-8.16 (m, 8H), 13.24 (s, 1H); ^{13}C NMR: δ = 25.2, 26.1, 34.5, 57.3, 112.6, 117.0, 117.9, 118.1 ,119.1, 122.9, 123.8, 125.0, 126.7, 129.5, 136.4, 139.8, 158.0; IR (KBr): ν_{max} (cm^{-1}): 3323 (NH and OH), 1664 (C=O); MS (EI, 70 eV): m/z 323 (M$^+$, 3), 225 (22), 126 (44), 77 (100), 83 (90); C, H, N-analysis calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99; found: C, 71.01; H, 6.98; N, 12.51.

2.1.4. N-tert-butyl-2-(2-hydroxyphenyl)-2-(pyridin-2-ylimino)acetamide (1d).

Brown crystal, mp.: 175-177^{0}C; ^1H NMR: δ = 1.29 (s, 9H), 5.42 (s, 1H), 6.87-8.17 (m, 8H), 13.24 (s, 1H); ^{13}C NMR: δ = 28.7, 52.9, 112.7, 116.9, 117.8, 118.1, 119.9, 122.9, 123.8, 125.0, 126.7, 129.5, 136.5, 139.8, 158.0; IR (KBr): ν_{max} (cm^{-1}): 3322 (NH and OH), 1667 (C=O); MS (EI, 70 eV): m/z 297 (M$^+$, 2), 204 (16), 100 (100), 77 (80); C, H, N-analysis calcd. for $C_{17}H_{19}N_3O_2$; C, 68.67, H, 6.44, N, 14.13; found: C, 68.37; H, 6.04; N, 14.59.

2.1.5. N-cyclohexyl-2-(2-hydroxyphenyl)-2-(pyrimidin-2-ylimino)acetamide (1e).

Yellow crystal, mp.: 193-195^{0}C; ^1H NMR: δ = 0.86-1.63 (m, 10H), 3.81-3.83 (m, 1H), 4.22 (d, J = 9 Hz, 1H), 6.89-8.48 (m, 7H), 12.03 (s, 1H); ^{13}C NMR: δ = 25.2, 26.1, 34.5, 57.3, 111.5, 112.6, 119.2, 119.9, 129.3, 131.4, 134.2, 139.3, 162.2, 164.1, 189.9; IR (KBr): ν_{max} (cm^{-1}): 3311 (NH and OH), 1665 (C=O); MS (EI, 70 eV): m/z 324 (M$^+$, 3), 231 (21), 126 (43), 77 (100); C, H, N-analysis calcd. for $C_{18}H_{20}N_4O_2$; C, 66.65; H, 6.21; N, 17.27; found: C,66.23; H, 6.32; N, 17.44.

2.1.6. N-tert-butyl-2-(2-hydroxyphenyl)-2-(pyrimidin-2-ylimino)acetamide (1f).

Bright yellow crystal, mp.: 187-189^{0}C; ^1H NMR: δ =1.45 (s, 9H), 4.21 (s, 1H), 6.89-8.48 (m, 7H), 12.03 (s, 1H); ^{13}C NMR: δ = 28.8, 52.6, 111.5, 112.59 ,119.2, 119.9, 129.3, 131.4, 134.2, 138.4, 162.2, 191.0; IR (KBr): ν_{max} (cm^{-1}): 3270 (NH and OH), 1680 (C=O); MS (EI, 70 eV): m/z 298 (M$^+$, 4), 205 (11), 93 (71), 77 (100); C, H, N-analysis calcd. for $C_{16}H_{18}N_4O_2$; C, 64.41; H, 6.08; N, 18.78; found: C, 64.86; H, 6.23; N, 18.34.

2.1.7. N-tert-butyl-2-(2-hydroxyphenyl)-2-(benzylimino)acetamide (1g).

Bright brown crystal, mp.: 79-81^{0}C; ^1H NMR: δ = 1.46 (s, 9H), 4.83 (bs, 3H), 6.75-7.70 (m, 9H), 11.54 (s, 1H); ^{13}C NMR: δ = 28.8, 44.9, 52.9, 112.7, 118.1, 119.1, 122.9, 123.8, 125.0, 158.0, 166.9; IR (KBr): ν_{max} (cm^{-1}): 3303 (NH and OH), 1675 (C=O); MS (EI, 70 eV): m/z 310 (M$^+$, 3), 210 (32), 145 (44), 77 (100), 57 (90); C, H, N-analysis calcd. for $C_{19}H_{22}N_2O_2$; C, 73.52; H, 7.14; N, 9.03 ; found: C, 73.07; H, 7.44; N, 9.38.

2.1.8. N-tert-butyl-2-(2-hydroxyphenyl)-2-(methylimino)acetamide (1h).

Bright brown crystal, mp.: 90-92^{0}C; ^1H NMR: δ = 1.24 (s, 9H), 3.54 (s, 3H), 5.20 (s, 1H), 7.19-8.18 (m, 4H), 13.27 (s, 1H); ^{13}C NMR: δ = 28.8, 44.9, 52.9, 112.7, 118.1, 119.1, 122.9, 123.8, 125.0, 158.0, 166.9; IR (KBr): ν_{max} (cm^{-1}): 3291 (NH and OH), 1670 (C=O); MS (EI, 70

eV): m/z 234 (M^+, 2), 141 (32), 72 (100), 77 (65); C, H, N-analysis calcd. for $C_{13}H_{18}N_2O_2$; C, 66.64; H, 7.74; N, 11.96; found: C, 66.99; H, 7.31; N, 12.35.

2.1.9. N-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-2-(phenylimino)acetamide (1i).

Bright brown crystal, mp.: 169-171^{0}C; ^{1}H NMR: δ =1.20-1.86 (m, 10H), 3.05-3.07 (m, 1H), 3.95 (s, 3H), 5.42 (s, 1H), 6.87-7.42 (m, 8H), 13.79 (s, 1H); ^{13}C NMR: δ = 25.3 , 26.1 ,34.4, 56.5, 57.4, 115.5, 116.7, 118.7, 122.0, 122.5, 126.4, 129.4, 146.6, 149.2, 153.0, 162.7, 158.8; IR (KBr): ν_{max} (cm^{-1}): 3296 (NH and OH), 1658 (C=O); MS (EI, 70 eV): m/z 352 (M^+, 4), 226 (9), 126 (45), 77 (100); C, H, N-analysis calcd. for $C_{21}H_{24}N_2O_3$; C, 71.57; H, 6.86; N, 7.95; found: C,71.99; H, 6.44; N, 7.65.

2.1.1.0 N-tert-butyl-2-(2-hydroxy-3-methoxyphenyl)-2-(phenylimino)acetamide (1j).

Brown crystal, mp.: 180-182^{0}C; ^{1}H NMR: δ = 1.20 (s, 9H), 3.98 (s, 3H), 5.43 (s, 1H), 6.88-7.40 (m, 8H), 13.79 (s, 1H); ^{13}C NMR: δ = 28.8, 53.0, 118.6, 119.5, 121.9, 122.5, 126.4, 129.3, 129.6, 131.2, 134.3, 146.8, 162.5, 168.5; IR (KBr): ν_{max} (cm^{-1}): 3296 (NH and OH), 1658 (C=O); MS (EI, 70 eV): m/z 326 (M^+, 2), 226 (24), 100 (65), 77 (100); C, H, N-analysis calcd. for $C_{19}H_{22}N_2O_3$; C, 69.92; H, 6.79; N, 8.58; found: C, 69.51; H, 6.39; N, 8.99.

2.1.11. N-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-2-(pyridin-2-ylimino)acetamide (1k).

Yellow crystal, mp.: 154-156^{0}C; ^{1}H NMR: δ =1.20-1.86 (m, 10H), 3.05-3.07 (m, 1H), 3.15 (bs, 1H), 3.98 (s, 3H), 6.86-8.18 (m, 7H), 13.22 (s, 1H); ^{13}C NMR: δ = 25.3, 26.1, 34,4, 56.5, 77,2, 77.5, 77.7, 111.6, 112.6, 117.1, 118.2, 118.6, 119.0, 122.9, 124.1, 124.9, 136.4,139.9, 147.8, 149.4; IR (KBr): ν_{max} (cm^{-1}): 3514 (NH and OH), 1637 (C=O); MS (EI, 70 eV): m/z 353 (M^+, 2), 126 (53), 106 (100), 77 (78); C, H, N-analysis calcd. for $C_{20}H_{23}N_3O_3$; C, 67.97 ; H, 6.56; N, 11.89; found: C, 67.53; H, 6.99; N, 11.45.

2.1.12. N-tert-butyl-2-(2-hydroxy-3-methoxyphenyl)-2-(pyridin-2-ylimino)acetamide (1l).

Yellow crystal, mp.: 204-206^{0}C; ^{1}H NMR: δ =1.21 (s, 9H), 3.15 (s, 1H), 3.98 (s, 3H), 6.86-8.18 (m, 7H), 13.22 (s, 1H); ^{13}C NMR: δ = 28.7, 52.9, 56.6, 111.5, 112.6, 117.1, 118.2, 119.0, 122.9, 124.9, 136.4, 139.9, 147.8, 149.4; IR (KBr): ν_{max} (cm^{-1}): 3290 (NH and OH), 1650 (C=O); MS (EI, 70 eV): m/z 327 (M^+, 4), 204 (14), 106 (56), 77 (100); C, H, N-analysis calcd. for $C_{18}H_{21}N_3O_3$; C, 66.04; H, 6.47; N, 12.84; found: C, 66.48; H, 6.04; N, 12.44.

2.1.13. N-cyclohexyl-2-(5-bromo-2-hydroxyphenyl)-2-(phenylimino)acetamide (1m).

Colorless crystal, mp.: 222-224^{0}C; ^{1}H NMR: δ = 1.23 (s, 10H), 3.05-3.07 (m, 1H), 5.12 (s, 1H), 6.73-7.42 (m, 8H), 13.35 (s, 1H); ^{13}C NMR: δ = 28.7, 29.6, 37.6, 60.7, 110.6, 118.6, 120.2, 121.9, 126.4, 133.3, 136.4, 146.5' 161.4, 162.2, 167.6; IR (KBr): ν_{max} (cm^{-1}): 3296 (NH and OH), 1658 (C=O); MS (EI, 70 eV): m/z 400 (M^+, 3), 172 (47), 126 (36), 77 (100); C, H, N-analysis calcd. for $C_{20}H_{21}BrN_2O_2$; C, 59.86; H, 5.27; N, 6.98; found: C, 60.01; H, 4.88; N, 6.66.

2.1.14. N-tert-butyl-2-(5-bromo-2-hydroxyphenyl)-2-(phenylimino)acetamide (1n).

Colorless crystal, mp.: 235-237^{0}C; ^{1}H NMR: δ =1.13 (s, 9H), 2.44 (s, 1H), 6.82-7.52 (m, 8H), 13.47 (s, 1H); ^{13}C NMR: δ = 28.6, 52.6, 110.6, 118.6, 120.2, 121.9, 126.4, 129.2, 133.3, 136.4, 146.5, 161.4, 162.2, 167.6; IR (KBr): ν_{max} (cm^{-1}): 3323 (NH and OH), 1631 (C=O); MS (EI, 70 eV): m/z 375 (M^+, 3), 153 (89), 100 (70), 77 (100); C, H, N-analysis calcd. for $C_{18}H_{19}BrN_2O_2$; C, 57.61; H, 5.10; N, 7.47; found: C, 57.11; H, 4.51; N, 7.98.

2.1.15. N-cyclohexyl-2-(5-bromo-2-hydroxyphenyl)-2-(pyridin-2-ylimino)acetamide (1o).

Yellow crystal, mp.: 209-211^{0}C; ^{1}H NMR: δ = 1.22-1.88 (m, 10H), 3.01-3.03 (m, 1H), 3.73 (dd, J = Hz, 1H), 6.93-7.55 (m, 7H), 13.31 (s, 1H); ^{13}C NMR: δ = 18.9, 25.2, 34.6, 57.4, 110.9, 113.0, 117.9, 119.6, 119.9, 122.8, 124.1, 125.4, 129.4, 131.9, 135.2, 139.9, 157.0; IR (KBr): ν_{max} (cm^{-1}): 3315 (NH and OH), 1670 (C=O); MS (EI, 70 eV): m/z 402 (M^+, 2), 274 (22), 126 (44), 83 (100), 77 (70); C, H, N-analysis calcd. for $C_{19}H_{20}BrN_3O_2$; C, 56.73; H, 5.01; N, 10.45; found: C, 56.32; H, 5.25; N, 10.69.

2.1.16. N-tert-butyl-2-(5-bromo-2-hydroxyphenyl)-2-(pyridin-2-ylimino)acetamide (1p).

Brown crystal, mp.: 218-220^{0}C; ^{1}H NMR: δ = 1.28 (s, 9H), 3.75 (s, 1H), 6.93-8.56 (m, 7H), 13.51 (s, 1H); ^{13}C NMR: δ = 30.9, 55.2, 108.9, 110.0, 119.7, 119.8, 121.0, 123.4,130.9, 135.7, 136.8, 139.0, 149.5, 161.3, 163.89; IR (KBr): ν_{max} (cm^{-1}): 3343 (NH and OH), 1680 (C=O) cm^{-1}; MS (EI, 70 eV): m/z 375 (M^+, 3), 196 (89), 100 (70), 77 (100); C, H, N-analysis calcd. for $C_{17}H_{18}BrN_3O_2$; C, 54.27; H, 4.82; N, 11.17; found: C, 54.53; H, 4.66; N, 11.01.

2.1.17. N-tert-butyl-2-(2-hydroxy-5-nitrophenyl)-2-(phenylimino)acetamide (1q).

Bright brown crystal, mp.: 183-185^{0}C; ^{1}H NMR: δ = 1.51 (s, 9H), 5.41 (s, 1H), 7.30-8.75 (m, 8H), 14.49 (s, 1H); ^{13}C NMR: δ = 28.8, 52.8, 118.3, 118.5, 118.8, 121.7, 128.5, 128.8, 128.8, 130.1, 140.4, 147.1, 161.0, 167.4; IR (KBr): ν_{max} (cm^{-1}): 3289 (NH and OH), 1673 (C=O); MS (EI, 70 eV): m/z 341 (M^+, 2), 241 (21), 100 (78), 77 (100); C, H, N-analysis calcd. for $C_{18}H_{19}N_3O_4$; C, 63.33; H, 5.61; N, 12.31; found: C, 62.98; H, 5.90; N, 12.22.

3. Results and Discussion

In the model experiment, the reaction smoothly went to completion when the imine, obtained from reaction of salicylaldehyde with aniline, was treated with cyclohexyl isocyanide in CH_3CN, and heated to reflux for 6 h. After evaporation of solvent under reduced pressure, the recrystalized solid from methanol was identified as 1a on the basis of analytical data (Scheme 1). The IR spectrum of 1a showed peaks at 3514, and 1637 cm^{-1} due to –OH, and –C=O groups, respectively. The ^1H NMR spectrum of 1a exhibited the characteristic multiplets at δ: 0.84-1.65 (10H) and 3.80-3.82 (1H) due to cyclohexyl and -CH-Ph protons, respectively. A doublet and a singlet appeared at δ: 5.45 (J = 8 Hz, 1H) and 13.31 (1H) for -NH and –OH groups, respectively. The ^{13}C NMR displayed four peaks at δ: 24.8 to 48.5 and nine peaks at δ: 116.7 to 146.9 due to aliphatic and aromatic carbons, respectively. Finally, two characteristic peaks appeared at δ: 162.5 and 168.5 for –C=N and –C=O groups, respectively. The MS (EI) spectrum revealed the molecular ion peak at m/z 322 corresponding to the molecular weight of 1a. The microelemental analysis of compound 1a was consistent with the molecular structure. Our later studies revealed that 1a could be prepared *via* a one-pot experiment if aniline, and cyclohexyl isocyanide are added successively to a solution of salicylaldehyde in CH_3CN. This experiment clearly indicates the implication of salicylaldehyde-aniline imine in the reaction.

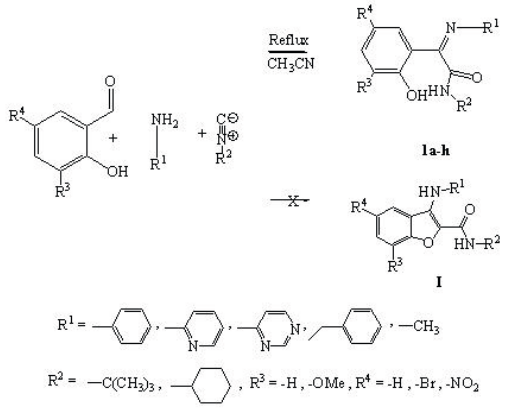
We then examined the scope of the amines that could participate in the coupling of cyclohexyl isocyanide or tert-butyl isocyanide with 2-hydroxybenzaldehyde derivatives through one-pot experiments (Scheme 2). The results are presented in Table 1. Three types of 2-hydroxybenzaldehyde derivatives worked with moderate to good efficiency, affording the desired products (Table 1). Inspection of the results, shown in Table 1, reveals that the reactions tolerate aniline affording the corresponding products in good yields (entries 1, 2, 9, 10, 13, 14, 17). On the other hand, utilization of heteroaryl amines leads to the formation of the relevant products, albeit with notably lower yields in some cases (entries 3-6, 11, 12, 15, 16). However, when aliphatic amines such as benzyl amine or methyl amine were used, the reaction became sluggish, affording products in poor yields of 10% and 12%, respectively (entries 7 and 8). Synthesis of 1j enabled the single crystal X-ray analysis to be performed. As shown in Fig. 1, the structure of 1j was further confirmed [23].

At the beginning of this study, we expected to obtain the N-alkyl-3-(aryllamino)-benzo[b] furan-2-carboxamides I from the reaction of 2-hydroxybenzaldehyde derivatives, amines and alkylisocyanides (Scheme 1). Obtaining 1a-q (Scheme 1) was a surprising outcome. Our surprise was tempered when a literature search disclosed that the similar compound III, has been employed as an important intermediate for preparing fungicides (Scheme 2) [24]. Compound III has been prepared from the reaction of alkyl (2-hydroxyphenyl)-oxoacetates II with a proper amount of methylamine (Scheme 2) [24]. Compounds II had been obtained in turn through the photo-Fries rearrangement of alkyl phenyl oxalates I as a minor product (Scheme 2) [25]. Therefore, the serendipitious outcome of 1a-q deserves some consideration.

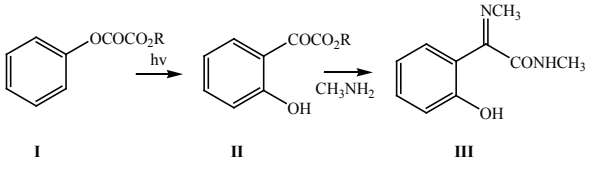
It is quite evident that obtaining products 1a-q supports the formation of N-alkyl-3-(aryllamino)-benzo[b] furan-2-carboxamides I as fleeting intermediates and their subsequent reaction with molecular oxygen. The following evidence could explain the reaction pathway for the formation of 1a-q.

(1) The reproduceability of 1a-q is guaranteed as long as the reaction is carried out under atmosphere.

(2) Implementation of the reaction of salicylaldehyde, aniline and cyclohexyl isocyanide under argon atmosphere afforded a complex mixture of products, amongst which 1a was not identified. This experiment clearly indicates the key role of molecular oxygen in the formation of 1a.



Scheme 1. Synthesis of compounds 1a-q.



Scheme 2. Structural similarity of III (obtained from II and I) with 1a

Table 1. Results of the synthesized 1a-q

Entry	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1		C_6H_{11}	H	H	1a	83
2		$(CH_3)_3C$	H	H	1b	75
3		C_6H_{11}	H	H	1c	58
4		$(CH_3)_3C$	H	H	1d	36
5		C_6H_{11}	H	H	1e	44
6		$(CH_3)_3C$	H	H	1f	40
7		$(CH_3)_3C$	H	H	1g	15
8	CH_3-	$(CH_3)_3C$	H	H	1h	14
9		C_6H_{11}	CH_3O	H	1i	81
10		$(CH_3)_3C$	CH_3O	H	1j	82
11		C_6H_{11}	CH_3O	H	1k	48
12		$(CH_3)_3C$-	CH_3O-	H	1l	45
13		C_6H_{11}	H	Br	1m	80
14		$(CH_3)_3C$	H	Br	1n	79
15		C_6H_{11}	H	Br	1o	75
16		$(CH_3)_3C$	H	Br	1p	63
17		$(CH_3)_3C$	H	NO_2	1q	53

[a]Isolated products.

(3) The 2-Hydroxy group present in salicylaldehyde has a vital role in the formation of 1a, since the reaction of benzaldehyde, primary amine and isocyanide has been reported to afford an indole derivative [26].

(4) That 1a might have been formed *via* the reaction of isocyanide with imine and subsequent reaction with water and oxidation of the obtained N-cyclohexyl-2-(2-hydroxyphenyl)-2-(phenylamino) acetamide to N-cyclohexyl-2-(2-hydroxyphenyl)-2-(phenylimino) acetamide does not seem to be a plausible pathway. The formation of 1a in dry acetonitrile rules out the implication of water. Moreover, implementation of the reaction in acetonitrile and water leads to a complex mixture of products.

(5) The final note, worth emphasizing, is the recently reported three-component condensation of salicylaldehyde, various o-aminophenols, and 2,6-dimethylphenylisocyanide affording 2-imino-1,4-benzoxazines (Scheme 3, pathway a) [27]. To cast light on the importance of the hydroxyl group of the

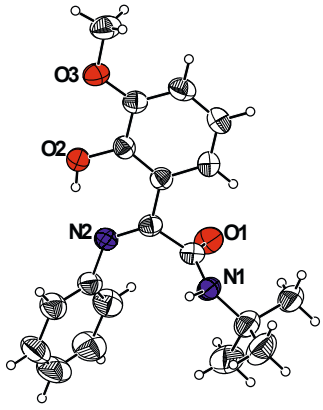
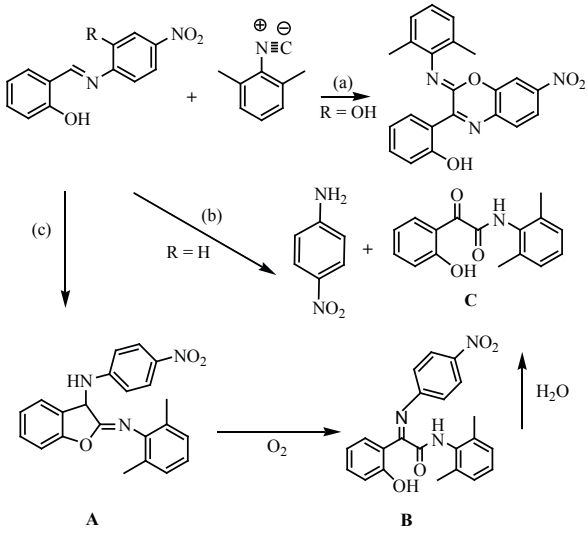
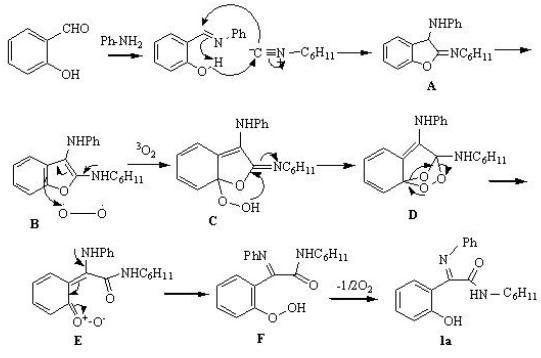


Figure 1. X-ray crystal structure of 1j.



Scheme 3. Proposed mechanism for the formation of C.



Scheme 4. Proposed mechanim for the formation of 1a

o-aminophenols in the formation of the benzoxazines, the authors have run the reaction with salicylaldehyde-p-nitroaniline Schiff base under nitrogen atmosphere. Isolation of t he 2-oxoacetamide derivative as the sole product has convinced the authors that the presence of the hydroxyl group of the o-aminophenol is a requirement for the generation of the benzoxazines (Scheme 3, pathway b) [27]. Although no explanation for the formation the 2-oxoacetamide derivative C has been suggested by the authors, we believe that it has been driven from the reaction of intermediate A with triplet oxygen probably during work-up, followed by hydrolysis of the 2-aryliminoacetamide derivative B during column chromatography (Scheme 3, pathway c).

To rationalize the reaction mechanism, it is postulated that treatment of salicylaldehyde with aniline leads to the formation of imine and nucleophilic attack of isocyanide to imine furnishes the iminolactone A as is shown in Scheme 4. Tautomerization of A to the fleeting 2-aminofuran B, and subsequent reaction with triplet oxygen affords hydroperoxide C. The formation of molozonide D followed by fragmentation to E and then to F would finally afford N-tert-butyl-2-(2-hydroxyphenyl)-2-(phenylimino)acetamide 1a. There are several reports in the literature for the fast conversion of iminolactones to 2-aminofurans. These quite unstable intermediates then undergo oxidation with triplet oxygen with mechanisms similar to that depicted in Scheme 4 [28-30].

4. Conclusion

In conclusion, *N*-alkyl-2-(2-hydroxyphenyl)-2-imino--acetamides containing three independently varying groups in one reaction were successfully prepared and identified through the 3CC of primary aromatic or heteroarylamines and isocyanides with bifunctional starting materials, such as 2-hydroxybenzaldehyde derivatives. It seems likely that products have been resulted from the preliminary formation of *N*-cyclohexyl-3-(phenylamino)-benzo[*b*]furan-2-carboxamide and subsequent oxidation with triplet oxygen.

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