# Reaction between isocyanides and salicylic acid or 3-hydroxy-2-naphthoic acid to produce benzo or naphtho-fused 2-(alkylamino)-1,3-dioxin-4-one derivatives

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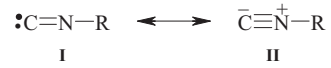
Protonation of isocyanides by salicylic acid or 3-hydroxy-2-naphthoic acid followed by addition of the conjugate anion of the acid to the resulting nitrilium cation and subsequent cyclisation of the iminoester intermediate formed leads to benzo or naphtho-fused 2-(alkylamino)-1,3-dioxin-4-one derivatives in excellent yields.

**Keywords:** isocyanides, salicylic acid, 3-hydroxy-2-naphthoic acid, addition reaction

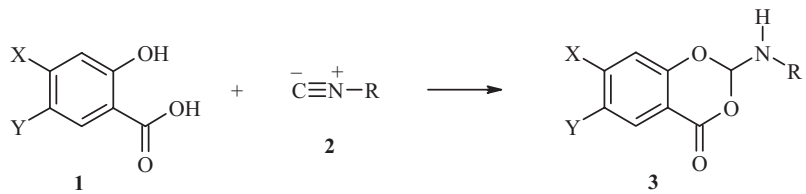
Isocyanides, as the only class of stable organic compounds with a two-valence carbon atom, are very reactive species and react with many functional groups through different mechanisms. On the basis of valence-bond theory, isocyanide functionality can be shown as two resonance forms **I** and **II** (Scheme 1). So, isocyanides have carbenic character on the basis of the resonance form **I** and nucleophilic character on the basis of the form **II**. In most addition reactions of isocyanides both the nucleophile and electrophile add to the α-carbon atom, and no species is added on the nitrogen atom.

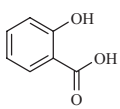
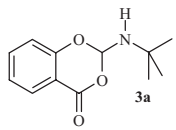
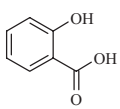
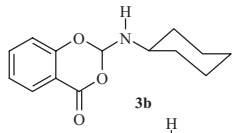
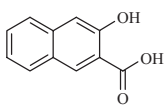
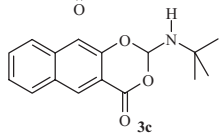
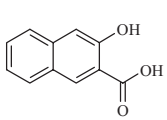
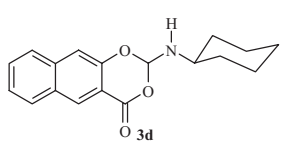
The addition reaction of different classes of chemical compounds to isocyanides has been of particular interest for many years. For example, the addition of hydrogen halides to alkyl isocyanides at low temperatures has been reported to produce *N*-alkyl formimidoyl halides.[1] The addition of hydrazoic acid to isocyanides was reported to produce tetrazole derivatives.[2,3] The addition of organic CH-acids, such as Meldrom's acid[4] or 1,1,1-trifluoro pentane-2,3-diones,[5] on isocyanides has also been reported. Isocyanides have been reported to react with two equivalents of carboxylic



**Scheme 1**

acids to afford the corresponding carboxylic formamides and carboxylic anhydrides.[1] Recently, it has been reported that the reaction of isocyanides with sulfonic acids leads to the corresponding sulfonamides.[6] A similar reaction was reported between isocyanides and carboxylic acids in methanol to yield the corresponding carboxamides.[7] In the course of our work with isocyanides,[8-10] we report here that the reaction between isocyanides and hydroxy carboxylic acids, such as salicylic acid or 3-hydroxy-2-naphthoic acid, produces benzo or naphtho-fused 2-(alkylamino)-1,3-dioxin-4-one derivatives in excellent yields. Thus the reaction between cyclohexyl isocyanide and salicylic acid in acetone at ambient temperature yields 2-(cyclohexyamino)benzo-1,3-dioxin-4-one in 88% yield. As shown in Scheme 2, similar products were obtained from the reaction of 3-hydroxy-2-naphthoic acid with isocyandes.



| Entry | Substrate | R | Product | Yield%* |
|---|---|---|---|---|
| 1 |  | t-Butyl |  | 90 |
| 2 |  | Cyclohexyl |  | 88 |
| 3 |  | t-Butyl |  | 87 |
| 4 |  | Cyclohexyl |  | 91 |

*Isolated yields

**Scheme 2**

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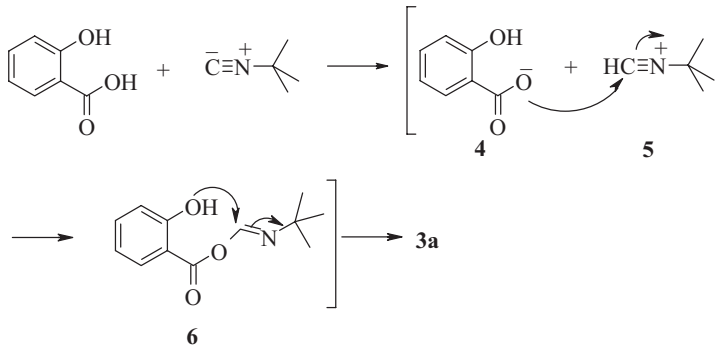


**Scheme 3**

The structure of compounds **3a–d** was deduced from their elemental analyses and IR, $^1$H NMR and $^{13}$C NMR spectroscopy. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The $^1$H NMR spectrum of **3a** exhibited two single sharp lines readily recognised as arising from *tert*-butyl (δ = 1.4) and methine (δ = 5.7) protons, along with signals (δ = 6.9–7.8) for aromatic protons. A single line was observed at δ = 10.7 which arises from the NH proton and disappeared by addition of $D_2O$ to the $CDCl_3$ solution of **3a.** The $^{13}$C NMR spectrum of **3a** showed 10 distinct resonances in agreement with the proposed structure.

The formation of compound **3a** can be rationalised as shown in Scheme 3. Protonation of t-butyl isocyanide by carboxyl functionality followed by the nucleophilic addition of the conjugate anion of salicylic acid **4** on the nitrilium cation **5** leads to iminoester **6** which then cyclises to product **3a**.

In summary, we report here that the addition reaction between isocyanides and salicylic acid or 3-hydroxy-2-naphthoic acid in acetone affords benzo or naphtho-fused 2-(alkylamino)-1,3-dioxin-4-one derivatives in excellent yields. The reaction is carried out under neutral conditions and starting materials are used without any need for purification or modification.

## Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on Shimadzu IR-470 spectrometer. $^1$H, and $^{13}$C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

*General procedure*

A solution of acid (2 mmol) and isocyanide (2 mmol) in acetone was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using hexane–ethyl acetate mixture as eluent. The solvent was removed under reduced pressure to afford the product.

*2-(tert-butylamino)-1,3-benzodioxin-4-one* **(3a)**: White powder, m.p. 69–70ºC, IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3360 (NH), 1667 (C=O). Analyses: Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%. Found: C, 65.2; H, 6.6; N, 6.4%. MS (*m/z*,%): 221 (8). $^1$H NMR (500 MHz, $CDCl_3$): δ 1.4 (9 H, s, 3 $CH_3$), 5.77 (1H, s, CH), 6.92–7.82 (4 H, m, 4 CH aromatic), 10.70 (1 H, s, NH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 29.03 (3 $CH_3$), 51.67 (C), 83.56 (CH), 112.97, 118.35, 119.62, 130.09, 136.44 and 162.47 (aromatic), 171.89 (C=O).

*2-(Cyclohexylamino)-1,3-dioxin-4-one* **(3b)**: White powder, m.p. 115–116ºC, IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3260 (NH), 1680 (C=O). Analyses: Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%. Found: C, 67.7; H, 6.9; N, 5.3%. MS (*m/z*, %): 247(7). $^1$H NMR (500 MHz, $CDCl_3$): δ 1.12–1.96 (10 H, m, 5 $CH_2$ of cyclohexyl), 3.83 (1H, m, CH of cyclohexyl), 5.81 (1H, CH), 6.92–7.83 (4 H, m, 4 CH aromatic), 10.67(1 H, s, NH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 25.14, 25.88, 33.32 (5 $CH_2$ of cyclohexyl), 48.65 (CH of cyclohexyl), 83.25 (CH), 112.94, 118.33, 119.62, 130.15, 136.45 and 162.46(aromatic), 171.75 (C=O).

*2-(Tert-butylamino)naphtho[2, 3-d][1,3]dioxin-4-one* **(3c)**: Yellow powder, m.p. 123–125ºC, IR(KBr) ($\nu_{max}$, cm$^{-1}$): 3395 (NH), 1674 (C=O). Analyses: Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%. Found: C, 70.9; H, 6.2; N, 5.4%. MS (*m/z*, %): 271 (8). $^1$H NMR (500 MHz, $CDCl_3$): δ 1.42 (9 H, s, 3 $CH_3$), 5.81 (1H, s, CH), 7.30–8.46 (6H, m, 6 CH aromatic), 10.35 (1 H, s, NH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 29.06 (3 $CH_3$), 51.76 (C), 83.83 (CH), 112.45, 114.82, 124.57, 126.80, 127.37, 129.53, 129.80, 132.71, 138.48 and 156.92 (aromatic), 171.78 (C=O).

*2-(Cyclohexylamino)naphtho[2,3-d][1,3]dioxin-4-one* **(3d)**: Yellow powder, m.p. 136–138ºC, IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3262 (NH), 1672 (C=O). Analyses: Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71%. Found: C, 72.9; H, 6.4; N, 4.4%. MS (*m/z*, %): 297(6). $^1$H NMR (500 $MH_Z$, $CDCl_3$): δ 1.19–1.86 (10 H, m, 5 $CH_2$ of cyclohexyl), 3.71 (1H, m, CH of cyclohexyl), 6.13 (1H, s, CH), 7.33–8.59 (6 H, m, 6 CH aromatic), 10.32 (1 H, s, NH). $^{13}$C NMR (125.8 $MH_Z$, $CDCl_3$): δ 24.70, 25.41, 32.84 (5 $CH_2$ of cyclohexyl), 48.84 (CH of cyclohexyl), 83.05 (CH), 111.65, 115.62, 124.44, 126.56, 127.40, 129.56, 129.63, 133.30, 138.08 and 156.76 (aromatic), 170.83 (C=O).

*Received 1 January 2008; accepted 5 February 2008*
*Paper 08/5020 doi: 10.3184/030823408X293215*

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