

[1 + 4]Cycloaddition of Isocyanides with 2-Acetyl-1,4-benzoquinone; a Convenient Synthesis of Isobenzofuran-4,7-quinones†

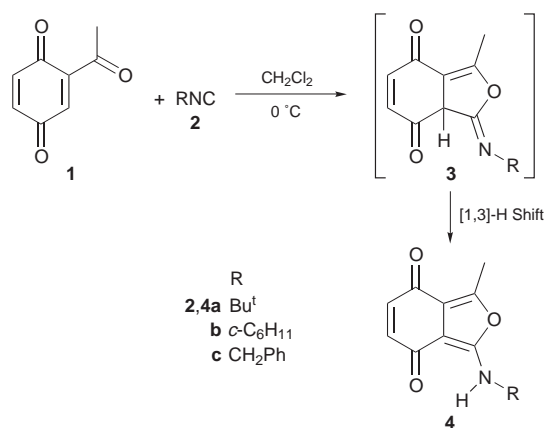
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Isocyanides undergo formal [1 + 4]cycloaddition with 2-acetyl-1,4-benzoquinone to afford isobenzofuran-4,7-quinone derivatives.

The [1 + 4]cycloaddition reactions of isocyanides with electrophilic heterodienes are of interest for the synthesis of heterocyclic compounds. Cycloaddition of isocyanides with *N*-acylimines,¹ azadienes,² diazadienes,³ α , β -unsaturated esters,⁴ α , β -unsaturated ketones,⁵ particularly with diethylaluminium chloride as a catalyst,⁶ nitroalkanes,⁷ vinyl isocyanates,⁸ 1,1,1,5,5,5-hexafluoropentane-2,4-dione⁹ and 3-(1-hydroxyethylidene)pentane-2,4-dione,¹⁰ have been described. The work reported here was undertaken in order to synthesise substituted isobenzofuran-4,7-quinones^{11–17} by the [1 + 4]cycloaddition of alkyl isocyanides, such as *tert*-butyl isocyanide, cyclohexyl isocyanide and benzyl isocyanide with 2-acetyl-1,4-benzoquinone **1**, as an electron-deficient hetero-1,3-diene. The [1 + 4]cycloaddition of isocyanides **2** with heterodiene **1** would afford compounds **3**, which isomerize to produce the stable *N*-substituted 1-alkylamino-3-methylisobenzofuran-4,7-quinones in high yields (Scheme 1).



Scheme 1

Structure **4** was assigned to isolated cycloadducts on the basis of their elemental analyses as well as their IR, ¹H, ¹³CNMR and mass spectral data. IR spectroscopy was applied to distinguish structure **4** from the initial cycloadducts **3**, which apparently isomerize to produce *N*-substituted isobenzofurane derivatives under the present reaction conditions. Thus, the IR spectra of the isolated products showed strong NH stretching bands at *ca.* 3280 cm⁻¹. Further evidence was obtained from ¹H NMR spectra which showed the absence of a methine hydrogen resonance.

Structure **4** was further confirmed by ¹H NMR spectra that revealed, in each case, a fairly broad singlet in the region of δ 3.7–4.8 which readily disappeared upon addition of D₂O. The mass spectra of the cycloadducts **4** are similar, as expected, and confirm their molecular weights. The ¹H NMR spectrum of **4a** exhibited three singlet signals arising from *tert*-butyl (δ 1.49), methyl (δ 2.58) and N–H [δ 3.71 (br)] along with two doublets [δ 6.62, (J = 10.3 Hz) and δ 6.77, (J = 10.3 Hz)], for the two vicinal CH groups. The proton decoupled ¹³C NMR spectrum of **4a** displayed eleven singlet signals. The ¹H and ¹³C NMR spectra of **4b** and **4c** are similar to that of **4a**. The structure assignments made on the basis of the NMR spectra of compounds **4a–c** were supported by their IR spectra; of special interest being N–H absorptions at 3285, 3270 and 3275 cm⁻¹ for **4a**, **4b** and **4c**, respectively.

In summary, the reaction of alkyl isocyanides with an electron deficient heterodiene, 2-acetyl-1,4-benzoquinone, provides a simple one-pot entry into the synthesis of stable *N*-substituted 1-alkylamino-3-methylisobenzofuran-4,7-quinones under mild reaction conditions using a simple experimental procedure.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500 and 125.77 MHz, respectively. The synthesis of 2-acetyl-1,4-benzoquinone **1** was carried out as described in the literature.¹⁸

General Procedure for the Preparation of *N*-Substituted 1-Alkylamino-3-methylisobenzofuran-4,7-quinones **4.**—To a magnetically stirred solution of **1** (150 mg, 1 mmol) in dichloromethane (10 ml) was added dropwise a mixture of *tert*-butyl isocyanide (0.113 μ l, 1 mmol) in dichloromethane (10 ml) at –20 °C over 10 min. The reaction mixture was allowed to warm to 0 °C, stirred for 24 h and the solvent removed under reduced pressure to afford the red product. For further purification, the product was recrystallized from 5% ethyl acetate–petroleum ether.

1-(*N*-*tert*-Butylamino)-3-methylisobenzofuran-4,7-quinone **4a:** yield 85%; mp 87–90 °C (decomp.). ν_{\max} (KBr)/cm⁻¹ 3285 (N–H), 1650 (C=O), 1622 (C=C). δ_{H} (CDCl₃, Me₄Si) 1.49 (9H, s, Bu^t), 2.58 (3H, s, Me), 3.71 (1H, br s, NH), 6.62 (1H, d, J = 10.3 Hz), 6.77 (1H, d, J = 10.3 Hz). δ_{C} (CDCl₃, Me₄Si) 13.42 (CH₃), 29.79 (CMe₃), 53.75 (CMe₃), 96.07 (C=C–N), 116.29 (C=C–O), 139.61 and 142.66 (2CH), 150.45 (C=C–N), 158.88 (C=C–O), 177.19 and 182.41 (2C=O). MS m/z (%) 233(M⁺, 21), 177(100), 162(55), 57(67) (Found: C, 66.81; H, 6.63; N, 5.90. C₁₃H₁₅O₃N requires: C, 66.93; H, 6.80; N, 6.00%).

1-(*N*-Cyclohexylamino)-3-methylisobenzofuran-4,7-quinone **4b:** yield 90%; mp 106–108 °C (decomp.). ν_{\max} (KBr)/cm⁻¹ 3270 (N–H), 1671 (C=O), 1635 (C=C). δ_{H} (CDCl₃, Me₄Si) 1.26–2.05 (11H, m, C₆H₁₁), 2.61 (3H, s, CH₃) 3.71 (1H, br s, NH), 6.62 (1H, d, J = 10.3 Hz), 6.77 (1H, d, J = 10.3 Hz). δ_{C} (CDCl₃, Me₄Si) 13.37 (CH₃), 24.66, 25.18 and 33.51 (3CH₂), 52.16 (CH), 95.16 (C=C–N), 116.71 (C=C–O), 139.53 (CH), 142.74 (CH), 150.22 (C=C–N),

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158.38, (C=C-O), 177.11 and 182.46 (2C=O). MS m/z (%) 259(M^+ , 44), 178(100), 97(2) (Found: C, 69.30; H, 6.51; N, 5.46. $C_{15}H_{17}O_3N$ requires: C, 69.48; H, 6.60; N, 5.40%).

1-(N-Benzylamino)-3-methylisobenzofuran-4,7-quinone **4c**: yield 80%; mp 88–90 °C (decomp.). ν_{\max} (KBr)/ cm^{-1} 3275 (N-H), 1660 (C=O), 1638 (C=C). δ_H ($CDCl_3$, Me_4Si) 2.57 (3H, s, CH_3), 4.66 (2H, s, CH_2), 4.86 (1H, br s, NH), 6.61 (1H, d, $J = 10.4$ Hz), 6.71 (1H, d, $J = 10.4$ Hz), 7.28–7.49 (5H, m, C_6H_5). δ_C ($CDCl_3$, Me_4Si) 13.35 (CH_3), 46.51 (CH_2), 95.49 (C=C-N), 116.73 (C=C-O), 127.95, 128.21, 128.99 and 136.49 (C_6H_5), 139.86 (CH), 142.45 (CH), 150.33 (C=C-N), 158.51 (C=C-O), 117.62 and 182.36 (2C=O). MS m/z (%) 267(M^+ , 21), 91(100), 65(17) (Found: C, 71.01; H, 4.84; N, 5.10. $C_{16}H_{13}O_3N$ requires: C, 71.9; H, 4.90; N, 5.23%).

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