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Synthesis and Dynamic NMR Study of Functionalized 1-(3-Furyl)-1*H*-indole-2,3-diones

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Summary. Protonation of the highly reactive 1:1 intermediates produced in the reaction between alkyl(aryl) isocyanides and dibenzoylacetylene by isatin, leads to vinylnitrilium cations, which undergo carbon-centered *Michael*-type addition with the conjugate base of the NH-acid to produce highly functionalized 1-(3-furyl)-1*H*-indole-2,3-diones. A dynamic NMR effect is observed in the ^{1}H NMR spectra of these compounds as a result of restricted rotation around the single bond linking the indole moiety and the furan system. The free-energy of activation ($\Delta G^{\#}$) for this process is 69–71 $\pm$ 2 kJ mol^{-1}.

Keywords. Dibenzoylacetylene; Isatin; Alkyl(aryl) isocyanides; Dynamic NMR.

Introduction

Polyfunctionalized furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products [1] and in important pharmaceuticals [2], but they can also be employed in synthetic chemistry as building blocks. For this reason, the synthesis of polysubstituted furans continues to attract the interest of many synthetic chemists. We now report an efficient synthetic route to polyfunctionalized furans using dibenzoylacetylene (*DBA*) and alkyl(aryl) isocyanides in the presence of isatin. Thus, the reaction between isocyanides **1** and *DBA* in the presence of isatin at ambient temperature in dry diethyl ether leads to 1-(3-furyl)-1*H*-indole-2,3-diones **2**.

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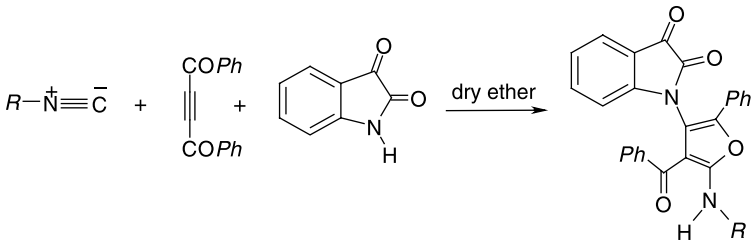
Results and Discussion

The reaction proceeded spontaneously at room temperature and produced **2** in excellent yield (Scheme 1). The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures.

On the basis of the well-established chemistry of isocyanides [3–6], it is reasonable to assume that compound **3** results from nucleophilic addition of **1** to *DBA* and subsequent protonation of the 1:1 adduct by isatin. Then, the positively charged ion **3** is attacked by the anion of the NH-acid **4** to produce the keteneimine **5**, which cyclizes, under the reaction condition employed, to produce **2** (Scheme 2).

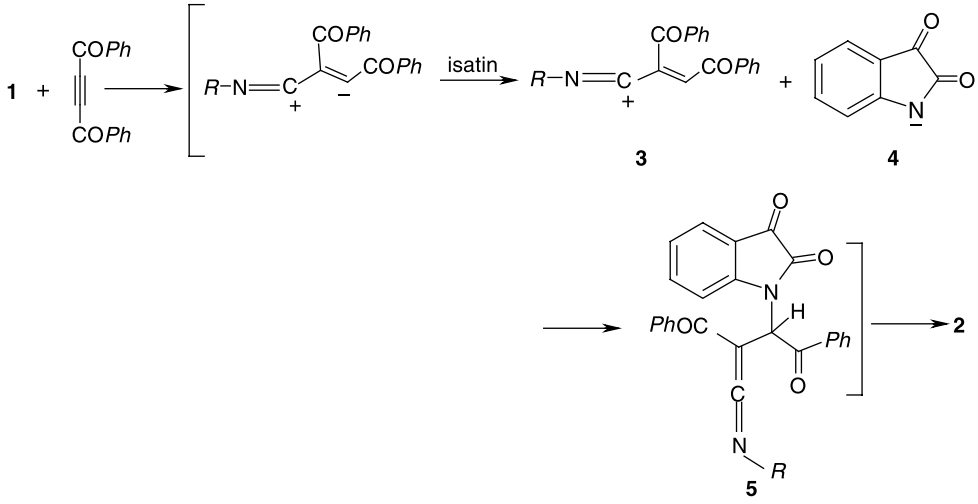
The ^{1}H NMR spectrum of **2a** in $CDCl_3$ showed a singlet at $\delta = 0.79$ ppm for the *tert*-butyl group. Because of restricted rotation around the *Ar*–N bond in these molecules, the CH_2 protons and the two methyl groups of the C*Me*$_2$ moiety are diastereotopic. Thus, the C*Me*$_2$ group exhibits two sharp singlets at $\delta = 1.18$ and 1.21 ppm while the methylene protons appear as an *AB* system at $\delta = 1.49$ ppm ($J_{AB} = 15.0$ Hz). The ^{1}H and ^{13}C NMR spectra of **2b**–**2d** are similar to those for **2a** except for the alkylamino moieties. The methylene protons of the benzyl group in **2b** are diasterotopic and exhibit an *ABX* ($J_{AB} = 14.2$ Hz, $J_{AX} = J_{BX} = 6.2$ Hz, $\delta_A = 4.52$ ppm, $\delta_B = 4.56$ ppm) system.



1 2

1, 2	R	Yield (%) of 2
a	1,1,3,3-Tetramethylbutyl	92
b	*Bn*	84
c	CH_2CO_2Et	85
d	*t-Bu*	84

Scheme 1



Scheme 2

Compounds **2a**–**2c** exhibit atropisomerism at ambient temperature because of hindered rotation around the carbon–nitrogen bond linking the isatin moiety and the furan ring system.

This becomes evident from the ^{1}H NMR spectrum of **2a** in $CDCl_3$ solution. At 20°C several sharp signals are present which become broad near 50°C (see Fig. 1). Increasing the temperature leads to coalescence of the methyl and methine signals.

Although an extensive lineshape analysis in relation to the dynamic NMR effect observed for **2a** was not undertaken in the present work, the variable temperature spectra are sufficient to calculate the free-energy barrier of activation for the restricted C–N bond rotation. From the coalescence of the methyl protons and using the expression $k = \pi\Delta\nu/\sqrt{2}$ [7], the first-order rate constant (k) was calculated (see Table 1).

Application of the absolute rate theory with a transmission coefficient of 1 gives a free energy of activation ($\Delta G^{\#}$) of 71 ± 2 kJ mol^{-1} for **2a**, where all known sources of errors are estimated and included [8]. Similar dynamic NMR effects were observed for the methylene protons of compounds **2b** and **2c**. Also **2d** will exhibit atropisomerism, it is just not visible in NMR.

In conclusion, the presented one-pot reaction leads to highly functionalized 1-(3-furyl)-1*H*-indole-2,3-diones. A dynamic NMR effect is observed in the ^{1}H NMR spectra of these compounds as a result of

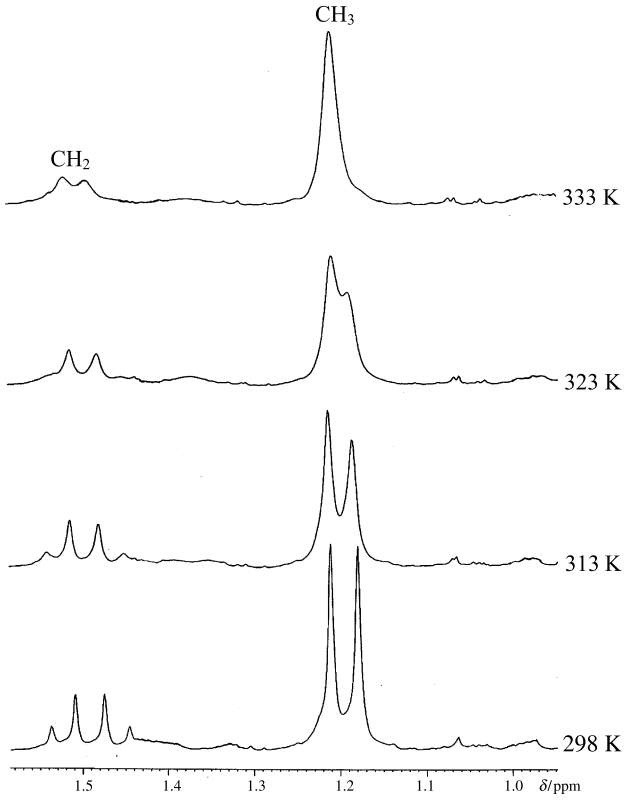


Fig. 1. Variable temperature 500 MHz ^{1}H NMR spectra of **2a** in $CDCl_3$

restricted rotation around the single bond linking the indole moiety and the furan system.

Experimental

DBA was prepared according to Refs. [9, 10]. Other chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz.

General Procedure for the Preparation of 1H-Indole-2,3-diones ***2***

To a magnetically stirred solution of 0.48 g *DBA* (2 mmol) and 0.30 g isatin (2 mmol) in 10 cm^3 CH_2Cl_2 were added 2 mmol of the alkyl(aryl) isocyanide at room temperature. The reaction mixture was then stirred for 30 h. The solvent was removed under reduced pressure and the viscous residue was purified by column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane: *EtOAc* (3:1) as eluent to give the product.

1-[4-Benzoyl-2-phenyl-5-[(1,1,3,3-tetramethylbutyl)amino]-3-furyl]-1H-indole-2,3-dione (**2a**, $C_{33}H_{32}N_2O_4$)

Orange powder, mp 166–168°C; yield 0.96 g, 92%. IR (KBr): $\bar{\nu} = 3465$, 1733, 1678, 1653, 1596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.79$ (s, CMe_3), 1.18 (s, CH_3), 1.21 (s, CH_3), 1.49 (dd, $J_{AB} = 15.0$ Hz, CH_2), 6.65 (d, $J = 7.2$ Hz, CH), 7.05 (t, $J = 7.3$ Hz, 2CH), 7.08 (d, $J = 7.1$ Hz, CH), 7.16 (t, $J = 7.9$ Hz, $2CH_{meta}$ of C_6H_5), 7.26 (s, N–H), 7.35 (t, $J = 7.4$ Hz, $2CH_{meta}$ of C_6H_5), 7.45 (t, $J = 7.2$ Hz, CH_{para} of C_6H_5), 7.51 (t, $J = 7.2$ Hz, CH_{para} of C_6H_5), 7.64 (d, $J = 7.3$ Hz, $2CH_{ortho}$ of C_6H_5), 7.87 (d, $J = 7.5$ Hz, $2CH_{ortho}$ of C_6H_5) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 29.7$ (CH_3), 30.1 (C), 31.6 ($3CH_3$), 31.9 (CH_3), 55.0 (CH_2), 63.0 (C–N), 93.4 and 110.8 (2C of furan), 122.9 (2CH of C_6H_4), 123.3, 124.5, 126.5, 127.7, 128.5, 128.9, 129.5, 131.2, 137.6, 141.4 ($2C_6H_5$ and C_6H_4), 150.6 (C–O), 159.9 (N–C–O), 164.0 (C=O), 180.2 and 185.9 (2C=O) ppm; MS (EI, 70 eV): m/z (%) = 520 (M^+, 10), 262 (25), 184 (15), 146 (10), 105 (100), 77 (45), 57 (100), 41 (42).

1-[4-Benzoyl-5-(benzylamino)-2-phenyl-3-furyl]-1H-indole-2,3-dione (**2b**, $C_{32}H_{22}N_2O_4$)

Yellow powder, mp 180–182°C; yield 0.84 g, 84%; IR (KBr): $\bar{\nu} = 3335$, 1730, 1663, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.54$ (ABX, $J_{AB} = 14.2$ Hz, $J_{AX} = J_{BX} = 6.2$ Hz, $\delta_A = 4.52$, $\delta_B = 4.56$), 6.93 (d, $J = 7.1$ Hz, CH), 7.13 (t, $J = 7.2$ Hz, 2CH), 7.16 (d, $J = 7.3$ Hz, CH), 7.19 (t, $J = 7.7$ Hz, $2CH_{meta}$ of C_6H_5), 7.25 (t, $J = 7.8$ Hz, $3CH_{meta}$), 7.31 (t, $J = 7.2$ Hz, $2CH_{ortho}$), 7.41 (t, $J = 7.7$ Hz, $2CH_{para}$ of C_6H_5), 7.45 (t, $J = 7.4$ Hz, CH_{para}), 7.53 (d, $J = 7.4$ Hz, $2CH_{ortho}$ of C_6H_5), 7.64 (d, $J = 7.2$ Hz, $2CH_{ortho}$ of C_6H_5), 8.19 (s, N–H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 44.3$ (CH_2–N), 94.3 and 110.6 (2C of furan), 122.5 (2CH of C_6H_4), 124.3, 125.5, 126.5, 127.6, 128.5, 128.9, 129.0, 132.7, 134.1, 135.8, 136.3, 137.0 ($3C_6H_5$ and C_6H_4), 146.9 (C–O), 152.1 (N–C–O), 161.8 (C=O), 188.8 and 197.2 (2C=O) ppm; MS (EI, 70 eV):

Table 1. Selected ^{1}H chemical shifts (500 MHz) and activation parameters of **2a**–**2c** in $CDCl_3$

	T_c/K	$\frac{\delta_{Me}}{ppm}$	$\frac{\delta_{Me}}{ppm}$	$\frac{\delta_{CH_a}}{ppm}$	$\frac{\delta_{CH_b}}{ppm}$	$\Delta\nu$/Hz	k_c/s^{-1}	$\frac{\Delta G^{\#}}{kJ\,mol^{-1}}$
2a	328	1.18	1.21			15	33	
	333			1.46	1.49	15	33	71 ± 2
2b	323			4.52	4.56	20	45	69 ± 2
2c	325			4.47	4.52	25	56	69 ± 2

m/z (%) = 498 (M^+, 5), 146 (25), 106 (65), 105(100), 91 (34), 77 (85), 57 (45).

Ethyl 2-[[3-benzoyl-4-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-5-phenyl-2-furyl]amino]acetate (**2c**, $C_{29}H_{22}N_2O_6$)
Pale yellow powder, mp 159–161°C; yield 0.84 g, 85%; IR (KBr): $\bar{\nu}$ = 3410, 1729, 1685, 1624 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, CH_3), 4.29 (q, J = 7.1 Hz, OCH_2), 4.49 (ABX, J_{AB} = 13.0 Hz, $J_{AX} = J_{BX}$ = 6.5 Hz, δ_A = 4.47, δ_B = 4.52), 6.96 (d, J = 7.1 Hz, CH), 7.01 (t, J = 7.2 Hz, 2CH), 7.04 (d, J = 7.3 Hz, CH), 7.12 (t, J = 7.5 Hz, $2CH_{meta}$ of C_6H_5), 7.31 (t, J = 7.8 Hz, $2CH_{meta}$ of C_6H_5), 7.50 (t, J = 7.3 Hz, CH_{para} of C_6H_5), 7.53 (t, J = 7.3 Hz, CH_{para} of C_6H_5), 7.60 (d, J = 7.5 Hz, $2CH_{ortho}$ of C_6H_5), 7.63 (d, J = 7.6 Hz, $2CH_{ortho}$ of C_6H_5), 8.79 (t, J = 5.6 Hz, NH. . .O=C) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.2 (Me), 44.2 (CH_2–N), 62.0 (OCH_2), 94.2 and 111.6 (2C of furan), 123.4 (2CH of C_6H_4), 124.3, 125.5, 126.5, 127.8, 128.3, 128.5, 129.0, 131.4, 138.6, 140.2 (C_6H_5 and C_6H_4), 150.1 (C–O), 158.1 (N–C–O), 164.9 and 168.6 (2C=O), 181.5 and 189.1 (2C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 494 (M^+, 4), 449 (38), 405 (62), 391 (54), 376 (21), 303 (18), 232 (28), 197 (8), 146 (68), 105(100), 76 (30), 57 (70).

1-[4-Benzoyl-5-(tert-butylamino)-2-phenyl-3-furyl]-1H-indole-2,3-dione (**2d**, $C_{29}H_{24}N_2O_4$)
Orange powder, mp 174–176°C; yield 0.78 g, 84%; IR (KBr): $\bar{\nu}$ = 3380, 1732, 1680, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.64 (s, 9H, CMe_3), 6.66 (d, J = 7.3 Hz, CH), 7.01 (t, J = 7.4 Hz, 2CH), 7.04 (d, J = 7.4 Hz, CH), 7.14 (t, J = 7.7 Hz, $2CH_{meta}$ of C_6H_5), 7.25 (t, J = 7.8 Hz, $2CH_{meta}$ of C_6H_5), 7.41 (t, J = 7.2 Hz, CH_{para} of C_6H_5), 7.47 (t, J = 7.3 Hz, CH_{para} of C_6H_5), 7.54 (d, J = 7.5 Hz, $2CH_{ortho}$ of C_6H_5), 7.63 (d, J = 7.6 Hz, $2CH_{ortho}$ of C_6H_5), 8.79 (s, N–H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.8 (CMe_3), 53.3 (CMe_3), 95.4 and 111.8 (2C of furan), 123.9 (2CH of C_6H_4), 124.3, 125.5, 126.5, 127.7, 128.0, 128.1, 129.0, 130.2, 138.6, 140.0 (C_6H_5 and C_6H_4), 150.6 (C–O), 157.9 (N–C–O), 163.0 (C=O), 181.2 and 188.9 (2C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 464 (M^+, 10), 409 (25), 408 (53), 407 (35), 303 (10), 260 (25), 232 (15), 197 (10), 105 (100), 76 (15), 57 (10).

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