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Synthesis of functionalized furan using multicomponent reaction of isatin

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Abstract: 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 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 **2** in the presence of isatin **3** at ambient temperature in NFM, leads to furan derivatives **4**.

Results and discussion

The reaction proceeded spontaneously at room temperature and produced **4** 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 **5** results from nucleophilic addition of **1** to DBA **2** and subsequent protonation of the 1:1 adduct by isatin **3**. Then, the positively charged ion **6** is attacked by the anion of the NH-acid **7** to produce the keteneimine **8**, which intramolecular cyclization, under the reaction condition employed, to produce the **4** (Scheme **2**).

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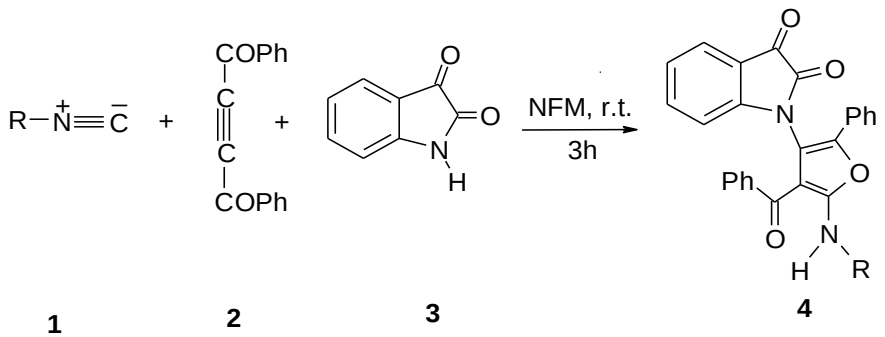
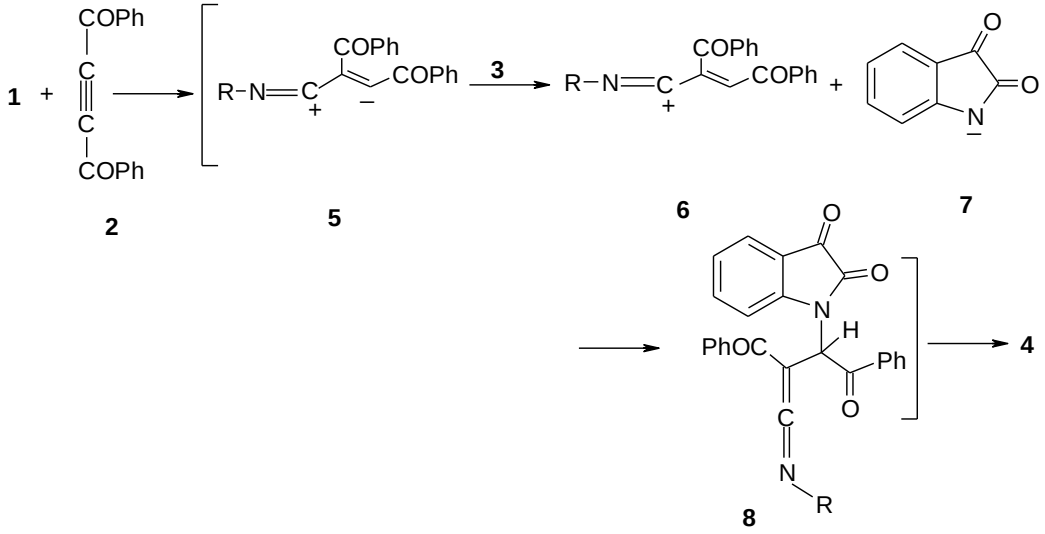


1, 4	R	Yield (%) of 4
a	1,1,3,3-Tetramethylbutyl	92
b	Bn	84
c	CH_2CO_2Et	85
d	^{t}Bu	84

Scheme 1: Synthesis of furan derivatives **4**



Scheme 2: proposed mechanism for the synthesis of furan derivatives **4**

The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed a singlet at δ = 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 CMe_2 moiety are diastereotopic. Thus, the CMe_2 group exhibits two sharp singlets at δ = 1.18 and 1.21 ppm while the methylene protons appear as a AB system at δ = 1.49 ppm (J_{AB} = 15.0 Hz). The ^{1}H and ^{13}C NMR spectra of **4b-d** are similar to those for **4a** except for the alkyl amino moieties. The methylene protons of benzyl group in **4b** are diasterotopic and exhibit an ABX (J_{AB} = 14.2 Hz, $J_{AX} = J_{BX}$ = 6.2 Hz, δ_A = 4.52, δ_B = 4.56 ppm) system.

Compounds **4a–4c** exhibit atropisomerism at ambient temperature because of hindered rotation around the carbon–nitrogen bond linking the isatin moiety and the furan ring system.

The most noteworthy feature of the ^{1}H NMR spectrum of **4a** in $CDCl_3$ solution at 20 ^{o}C is the presence of several sharp signals (see Fig. 1). Near 50 ^{o}C, the sharp lines become broad. Increasing the temperature leads to coalescence of the methyl and

methine signals. This dynamic effect is interpreted in terms of a restricted rotation around the single bond linking the indol moiety and the furan ring system.

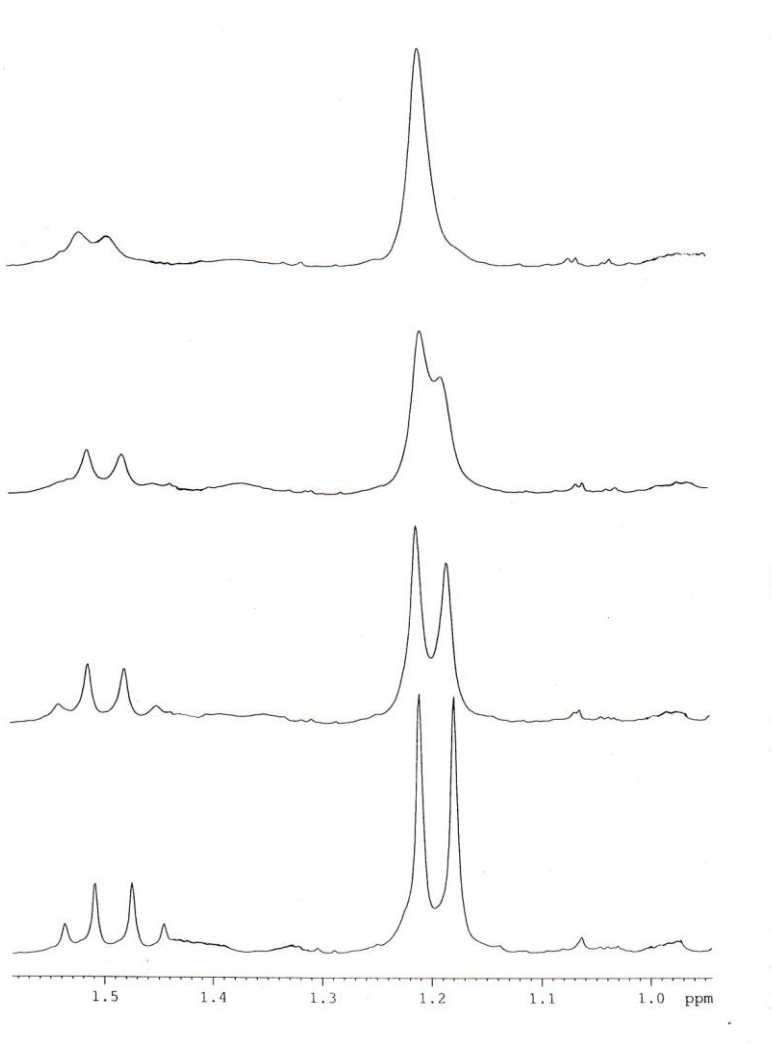


Figure 1. Variable temperature 500 MHz ^{1}H NMR spectra of **4a** in $CDCl_3$

Although an extensive lineshape analyses in relation to the dynamic NMR effect observed for **4a** 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 kJ mol^{-1} for **4a**, where all known sources of errors are estimated and included [8]. Similar dynamic NMR effects were observed for the methylene protons of compounds **4b** and **4c**.

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

Table 1. Selected ^{1}H chemical shifts (500 MHz) and activation parameters of **4a-4c** in $CDCl_3$

	T_C / K	δ_{CH3} ppm		δ_{CH_a} ppm	δ_{CH_b} ppm	$\Delta\nu$ / Hz	K / s^{-1}	$\Delta G^{\neq}$ kJ mol^{-1}
2a	328	1.18	1.21			15	33	
	333			1.46	1.49	15	33	71
2b	323			4.52	4.56	20	45	69
2c	325			4.47	4.52	25	56	69

Conclusion

In summary, the reaction of propiolates with trialkyl(aryl) phosphites in the presence of isatin, provides a simple one-pot synthesis of stable dialkyl(aryl) phosphorylsuccinates of potential synthetic and pharmaceutical interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

Dibenzoylacetylene 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 the 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-MATT 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.

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

Typical procedure: To a magnetically stirred solution of 0.48 g dibenzoylacetylene (2 mmol) and 0.30 g isatin (2 mmol) in 10 mL CH_2Cl_2 was added 0.30 mL 1,1,3,3-tetramethylbutyl isocyanide (2 mmol) 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 **2a**. Orange powder, m.p. 166-168°C,; yield 0.96 g, 92%. IR (KBr): ν = 3465, 1733, 1678, 1653, 1596 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (9 H, s, CMe_3), 1.18 (3 H, s, CH_3), 1.21 (3 H, s, CH_3), 1.49 (2 H, dd, J_{AB} = 15.0 Hz, CH_2), 6.65 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.05 (2 H, t, $^3J_{HH}$ = 7.3 Hz, 2 CH), 7.08 (1 H, d, $^3J_{HH}$ = 7.1 Hz, CH), 7.16 (2 H, t, $^3J_{HH}$ = 7.9 Hz, 2 CH_{meta} of C_6H_5), 7.26 (1H, s, N-H), 7.35 (2 H, t, $^3J_{HH}$ = 7.4 Hz, 2 CH_{meta} of C_6H_5), 7.45 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH_{para} of C_6H_5), 7.51 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH_{para} of C_6H_5), 7.64 (2 H, d, $^3J_{HH}$ = 7.3 Hz, 2 CH_{ortho} of C_6H_5), 7.87 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH_{ortho} of C_6H_5) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.7 (CH_3), 30.1 (C), 31.6 (3 CH_3), 31.9 (CH_3), 55.0 (CH_2), 63.0 (C-N), 93.4 and 110.8 (2 C of furan), 122.9 (2 CH of C_6H_4), 123.3, 124.5, 126.5, 127.7, 128.5, 128.9, 129.5, 131.2, 137.6, 141.4 (2 C_6H_5 and C_6H_4), 150.6 (C–O), 159.9 (N–C–O), 164.0 (C=O), 180.2 and 185.9 (2 C=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, m.p. 180-182°C, yield 0.84 g, 84%. IR (KBr): ν = 3335, 1730, 1663, 1595cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54 (ABX, J_{AB} = 14.2 Hz, J_{AX} = J_{BX} = 6.2 Hz, δ_A = 4.52, δ_B = 4.56), 6.93 (1 H, d, $^3J_{HH}$ = 7.1 Hz, CH), 7.13 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.16 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.19 (3 H, t, $^3J_{HH}$ = 7.7 Hz, 2 CH_{meta} of C_6H_5), 7.25 (3 H, t, $^3J_{HH}$ = 7.8 Hz, 3 CH_{meta}), 7.31 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_{ortho}), 7.41 (2 H, t, $^3J_{HH}$ = 7.7 Hz, 2 CH_{para} of C_6H_5), 7.45 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para}), 7.53 (2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH_{ortho} of C_6H_5), 7.64 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH_{ortho} of C_6H_5), 8.19 (1 H, s, N-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 44.3 (CH_2-N), 94.3 and 110.6 (2 C of furan), 122.5 (2 CH 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 (3 C_6H_5 and C_6H_4), 146.9 (C–O), 152.1 (N–C–O), 161.8 (C=O), 188.8 and 197.2 (2 C=O) ppm. MS (EI, 70 eV): *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, m.p. 159-161°C, yield 0.84 g, 85%. IR (KBr): ν = 3410, 1729, 1685, 1624 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.29 (2 H, q, $^3J_{HH}$ = 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 (1 H, d, $^3J_{HH}$ = 7.1 Hz, CH), 7.01 (2 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.04 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.12 (2 H, t, $^3J_{HH}$ = 7.5 Hz, 2 CH_{meta} of C_6H_5), 7.31 (2 H, t, $^3J_{HH}$ = 7.8 Hz, 2 CH_{meta} of C_6H_5), 7.50 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of C_6H_5), 7.53 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of C_6H_5), 7.60 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH_{ortho} of C_6H_5), 7.63 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH_{ortho} of C_6H_5), 8.79 (t, NH...O=C, $^3J_{HH}$ = 5.6 Hz) 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 (2 C of furan), 123.4 (2 CH of C_6H_4), 124.3, 125.5, 126.5, 127.8, 128.3, 128.5, 129.0, 131.4, 138.6, 140.2 (2 C_6H_5 and C_6H_4), 150.1 (C–O), 158.1 (N–C–O), 164.9 and 168.6 (2 C=O), 181.5 and 189.1 (2 C=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, m.p. 174-176°C, yield 0.78 g, 84%. IR (KBr): ν = 3380, 1732, 1680, 1606 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.64 (9 H, s, CMe_3), 6.66 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.01 (2 H, t, $^3J_{HH}$ = 7.4 Hz, 2 CH), 7.04 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.14 (2 H, t, $^3J_{HH}$ = 7.7 Hz, 2 CH_{meta} of C_6H_5), 7.25 (2 H, t, $^3J_{HH}$ = 7.8 Hz, 2 CH_{meta} of C_6H_5), 7.41 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH_{para} of C_6H_5), 7.47 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of C_6H_5), 7.54 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH_{ortho} of C_6H_5), 7.63 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH_{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 (2 C of furan), 123.9 (2 CH of C_6H_4), 124.3, 125.5, 126.5, 127.7, 128.0, 128.1, 129.0, 130.2, 138.6, 140.0 (2 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 (2 C=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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