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Synthesis of iminofurane derivatives using one pot multicomponent reaction: Dynamic NMR Study

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Abstract: In this research the reaction between alkyl(aryl) isocyanides, dibenzoylacetylene, ninhydrin and ammonium acetate leads to production of highly functionalized inminofuranes. 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 75-83 kJ mol^{-1}.

Keywords: Dibenzoylacetylene, Ninhydrin, Alkyl(aryl) isocyanides; Dynamic NMR, Ammonium acetate.

Introduction

In general, multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library syntheses, thus are finding increasing use in the discovery process for new drugs and agrochemicals [1-7]. Polyfunctionalized furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products [8] and in important pharmaceuticals [9-12], 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.

In recent years, the research into novel active organic substances and into the design of molecular electronic devices has attracted considerable interest [13-17]. Usually the compounds, which have antioxidant ability due to their reductive properties and chemical structure, remove the negative effect of free radicals and use as transitional metals chelators. Also, these compounds could be avoid or decrease many sicknesses such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer. Herein, we describe an efficient procedure for direct synthesis of polyfunctionalized iminofurans using dibenzoylacetylene, alkyl(aryl) isocyanides, ammonium acetate and ninhydrine. Thus, the reaction between isocyanides **3**, DBA **4**, ninhydrin **1** and ammonium acetate **2** at ambient temperature under solvent-free conditions leads to iminofuranes **5** in high yields (Scheme **1**).

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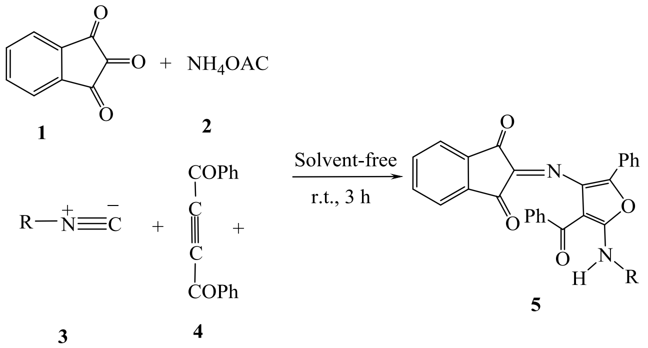
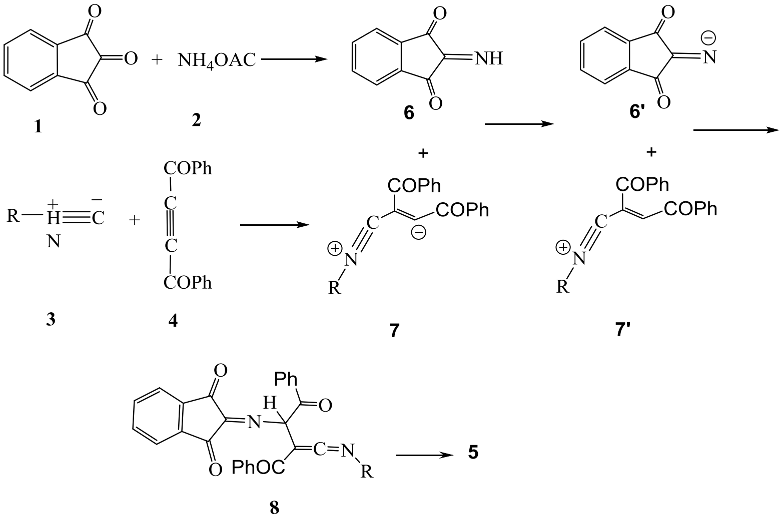


Scheme 1: Direct synthesis of iminofurans **5**

Result and Discussion

We describe an efficient procedure for direct synthesis of polyfunctionalized iminofurans using dibenzoylacetylene, alkyl(aryl) isocyanides, ammonium acetate and ninhydrine. Thus, the reaction between between isocyanides **3**, DBA **4**, ninhydrin **1** and ammonium acetate **2** at ambient temperature under solvent-free conditions leads to iminofuranes **5** in high yields (Scheme **1**). The reaction proceeded spontaneously at room temperature and produced **5** in excellent yield. The nature of these compounds as 1:1:1:1 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 **3** to DBA **4** and subsequent reaction with of the 1:1 adduct by ninhydrin and ammonium acetate. Then, the positively charged ion **7** is attacked by the anion of the NH-acid **6** to produce the keteneimine **8**, which cyclize, under the reaction condition employed, to produce the **5** (Scheme **2**).

The ^{1}H NMR spectrum of **5a** 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).



Scheme 2: Tentative mechanism for synthesis of compounds **5**

The ^{1}H and ^{13}C NMR spectra of **5b-d** are similar to those for **4a** except for the alkyl amino moieties. The methylene protons of benzyl group in **5b** 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 **5a–5c** 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 **5a** in $CDCl_3$ solution at 20 °C is the presence of several sharp signals (Figure **1**). Near 50 °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.

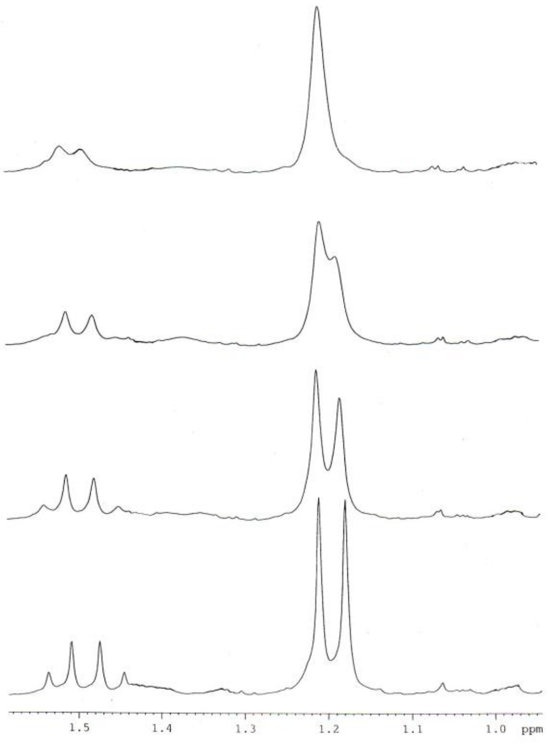


Figure 1: Variable temperature 500 MHz ^{1}H NMR spectra of **5a** in $CDCl_3$

Antioxidant ability evaluation of imidazol oxazin by utilizing of free radical of DPPH

Trapping of DPPH radical test is generally employed for the antioxidant capacity approval or strength of compounds for getting of selected iminofurans free radical and investigation of percentage of inhibit oxidation of them in foods and biological structures. In these evaluation, antioxidant capacity of synthesized iminofurans was determined by taking the hydrogen atom or one electron by DPPH radical and order of antioxidant ability of these compounds are basis of percentage of DPPH radical free trapping. The electron or hydrogen donating power of compounds **5a-5d** to the radical of DPPH determined the antioxidant ability of them. The radical of DPPH absorption was decreased from 517 nm when give one electron or hydrogen from antioxidant or a radical typs. In this work, the ability of iminofurans **5a-5d** as antioxidant was evaluated relative to BHT and TBHQ as standard and prepared antioxidant with different concentrations. Overall, the power of DPPH trapping was obtained TBHQ>BHT>**5b**>**5a**>**5c**>**5d** (Figure **2**).

As seen in Figure **2**, the novel prepared iminofuran in all concentrations have a good activity relative to BHT and TBHQ. In between of prepared iminofurans comopound **5b** showed vrey good activity to radical trapping relative to BHT and TBHQ as standards antioxidant.

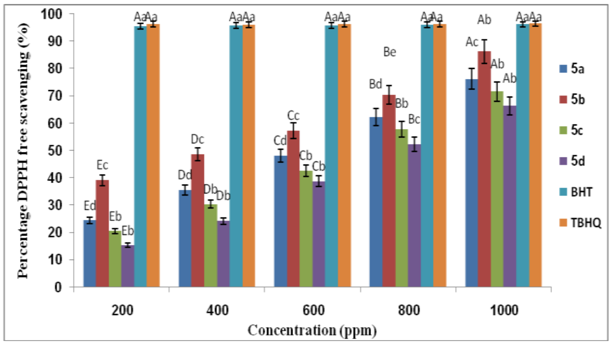


Figure 2. The activity of iminofurans **5a-5d** for radical scavenging

The potential of synthesized indoles by Ferric ions (Fe^{3+}) reducing

The reducing ferric ions (Fe^{3+}) ability of some synthesized iminofurans such as **5a-5d** are calculated based on the quantity reducing of $Fe^{3+/}$ferricyanide to the Fe^{2+}/ ferrous at 700 nm. As seen in Figure 3, compound **5b** was shown good ability of reducing than to BHT and TBHQ as standard antioxidants. The reducing activity trend of the samples was as follows: **TBHQ>BHT>5b>5d>5a>5c.** The outcomes are displayed in Figure 3.

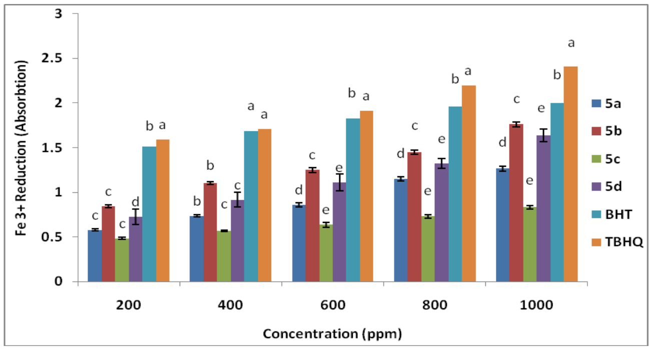


Figure 3. Antioxidant power of compounds **5a-5d** basis as ferric ions (Fe^{3+}) reducing.

Conclusion

In conclusion, the reaction of deficient acetylenic compounds with isocyanides and isatin in the presence led to indoles in excellent yields. 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 apparatus. 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 (4a):

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 **5a**. 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, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.05 (2 H, t, $^{3}J_{HH}$ = 7.3 Hz, 2 CH), 7.08 (1 H, d, $^{3}J_{HH}$ = 7.1 Hz, CH), 7.16 (2 H, t, $^{3}J_{HH}$ = 7.9 Hz, 2 CH_{meta} of C_6H_5), 7.26 (1H, s, N-H), 7.35 (2 H, t, $^{3}J_{HH}$ = 7.4 Hz, 2 CH_{meta} of C_6H_5), 7.45 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH_{para} of C_6H_5), 7.51 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH_{para} of C_6H_5), 7.64 (2 H, d, $^{3}J_{HH}$ = 7.3 Hz, 2 CH_{ortho} of C_6H_5), 7.87 (2 H, d, $^{3}J_{HH}$ = 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 (5b):

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,

$^{3}J_{HH}$ = 7.1 Hz, CH), 7.13 (2 H, t, $^{3}J_{HH}$ = 7.2 Hz, 2 CH), 7.16 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.19 (3 H, t, $^{3}J_{HH}$ = 7.7 Hz, 2 CH$_{meta}$ of C_6H_5), 7.25 (3 H, t, $^{3}J_{HH}$ = 7.8 Hz, 3 CH$_{meta}$), 7.31 (2 H, t, $^{3}J_{HH}$ = 7.2 Hz, 2 CH$_{ortho}$), 7.41 (2 H, t, $^{3}J_{HH}$ = 7.7 Hz, 2 CH$_{para}$ of C_6H_5), 7.45 (1 H, t, $^{3}J_{HH}$ = 7.4 Hz, CH$_{para}$), 7.53 (2 H, d, $^{3}J_{HH}$ = 7.4 Hz, 2 CH$_{ortho}$ of C_6H_5), 7.64 (2 H, d, $^{3}J_{HH}$ = 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_6 H_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 (5c):

Pale yellow powder, m.p. 159-161°C, yield 0.84 g, 85%. IR (KBr): ν = 3410, 1729, 1685, 1624 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH_3), 4.29 (2 H, q, $^{3}J_{HH}$ = 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, $^{3}J_{HH}$ = 7.1 Hz, CH), 7.01 (2 H, t, $^{3}J_{HH}$ = 7.2 Hz, 2 CH), 7.04 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.12 (2 H, t, $^{3}J_{HH}$ = 7.5 Hz, 2 CH$_{meta}$ of C_6H_5), 7.31 (2 H, t, $^{3}J_{HH}$ = 7.8 Hz, 2 CH$_{meta}$ of C_6H_5), 7.50 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH$_{para}$ of C_6H_5), 7.53 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH$_{para}$ of C_6H_5), 7.60 (2 H, d, $^{3}J_{HH}$ = 7.5 Hz, 2 CH$_{ortho}$ of C_6H_5), 7.63 (2 H, d, $^{3}J_{HH}$ = 7.6 Hz, 2 CH$_{ortho}$ of C_6H_5), 8.79 (t, NH...O=C, $^{3}J_{HH}$ = 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 (5d):

Orange powder, m.p. 174-176°C, yield 0.78 g, 84%. IR (KBr): ν = 3380, 1732, 1680, 1606 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (9 H, s, CMe_3), 6.66 (1 H, d, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.01 (2 H, t, $^{3}J_{HH}$ = 7.4 Hz, 2 CH), 7.04 (1 H, d, $^{3}J_{HH}$ = 7.4 Hz, CH), 7.14 (2 H, t, $^{3}J_{HH}$ = 7.7 Hz, 2 CH$_{meta}$ of C_6H_5), 7.25 (2 H, t, $^{3}J_{HH}$ = 7.8 Hz, 2 CH$_{meta}$ of C_6H_5), 7.41 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH$_{para}$ of C_6H_5), 7.47 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH$_{para}$ of C_6H_5), 7.54 (2 H, d, $^{3}J_{HH}$ = 7.5 Hz, 2 CH$_{ortho}$ of C_6H_5), 7.63 (2 H, d, $^{3}J_{HH}$ = 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 (C*Me*$_3$), 53.3 (*C*Me$_3$), 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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