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Catalyst free synthesis of indole derivatives via multicomponent reaction of aniline under solvent-free conditions

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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 indole-2,3-diones.

Keywords: Activated acetylenic compounds, Aniline, Alkyl(aryl) isocyanides.

Introduction

Multicomponent Reaction (MCRs) open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [1, 2]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [3-5]. Polyfunctionalized furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products [6] and in important pharmaceuticals [7], 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. Herein, in continuing research of my study for finding out new process for generation of valuable organic compounds [8-15], we describe an efficient procedure for direct synthesis of polyfunctionalized furans using aniline, diethyl oxalate, dibenzoylacetylene (DBA) and alkyl(aryl) isocyanides in room temperature under solvent-free conditions. Thus, the reaction between aniline **1**, diethyloxalate **2**, isocyanides **3** and activated acetylenic compounds **4** at ambient temperature under solvent-free conditions leads to 1H-indole-2,3-diones **5** (Scheme **1**).

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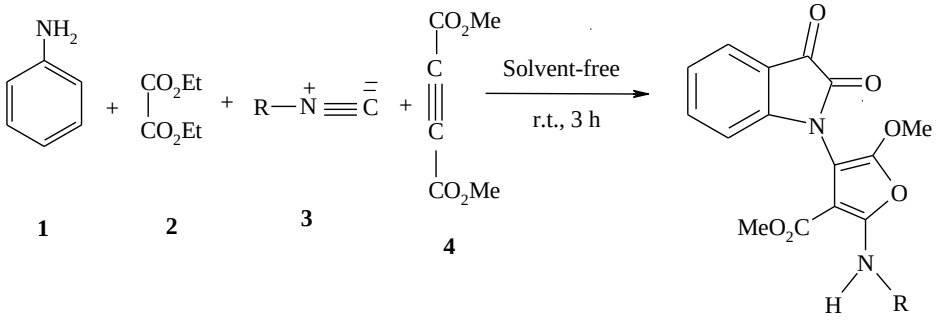


5	R	Yield (%) of **5**
a	1,1,3,3-Tetramethylbutyl	92
b	Bn	84
c	CH_2CO_2Et	85
d	^{t}Bu	84

Scheme 1: Direct synthesis of 1H-indole-2,3-diones.

Result and Discussion

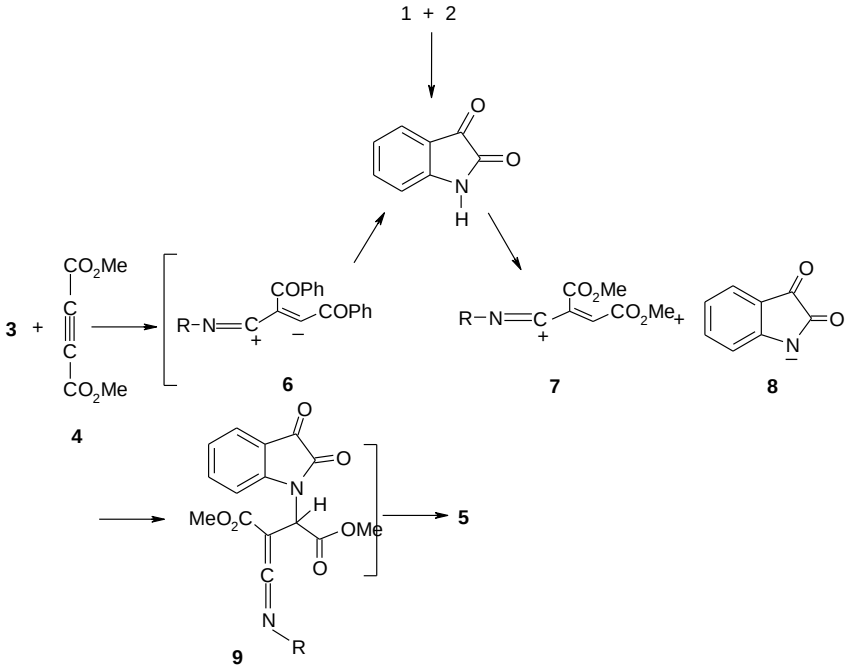
We describe an efficient procedure for direct synthesis of polyfunctionalized furans using the reaction of aniline **1**, diethyloxalate **2**, isocyanides **3** and activated acetylenic compounds **4** at ambient temperature under solvent-free conditions, leads to 1H-indole-2,3-diones **5** (Scheme **1**). The reaction proceeded spontaneously at room temperature and produced **5** in excellent yield. 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 [19-21], it is reasonable to assume that compound 3 results from nucleophilic addition of **1** to DBA **2** 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 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). The ^{1}H and ^{13}C NMR spectra of **5b-d** are similar to those for **5a** 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.

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

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.



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

Preparation of 1-[4-benzoyl-2-phenyl-5- [(1,1,3,3-tetramethylbutyl)amino)-3-furyl]-1H-indole-2,3-dione (5a):

Typical procedure: To a magnetically stirred mixture of aniline **1** (2 mmol), diethyloxalate **2** (2 mmol) and activated acetylenic compounds **4** (2 mmol) was added isocyanide **3** (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}. ^1H 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 (5b):

Yellow powder, m.p. 180-182°C, yield 0.84 g, 84%. IR (KBr): ν = 3335, 1730, 1663, 1595cm^{-1}. ^1H 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_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}. ^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 (5d):

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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