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Reaction between alkyl isocyanides and dibenzoylacetylene in the presence of strong NH-acids: synthesis of highly functionalized aminofurans

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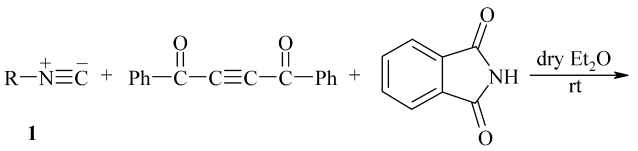
Abstract—Protonation of the highly reactive 1:1 intermediates produced in the reaction between alkyl isocyanides and dibenzoylacetylene by saccharin, phthalimide, or 4-methyl-5-nitroimidazole, leads to vinylnitrilium cations, which undergo carbon-centered Michael type addition with the conjugate base of the NH-acid to produce highly functionalized aminofuran derivatives.

Polysubstituted 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. The formation of a carbon–carbon bond at the α-position to a nitrogen atom is of importance for the elaboration of amines and, in particular, the synthesis of nitrogen-containing natural products and biologically active compounds.[3] We now report an efficient synthetic route to polysubstituted furans using dibenzoylacetylene and alkyl isocyanides in the presence of a NH-acid such as saccharin, phthalimide or 4-methyl-5-nitroimidazole. Thus, the reaction between dibenzoylacetylene and alkyl isocyanides in the presence of heterocyclic NH-acids at ambient temperature in dry diethyl ether, leads to highly functionalized aminofurans.

The reaction of dibenzoylacetylene with alkyl isocyanides in the presence of phthalimide, proceeded spontaneously at room temperature in dry diethyl ether and produced 2-[4-benzoyl-5-(alkylamino)-2-phenyl-3-furyl]-1*H*-isoindole-1,3-(2*H*)-dione (**2**) and 2-{(*Z*)-1-benzoyl-2-[(alkylimino)-methyl]-3-oxo-3-phenyl-1-propenyl}-1*H*-isoindole-1,3-(2*H*)-dione (**3**) in a 2:1 ratio (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



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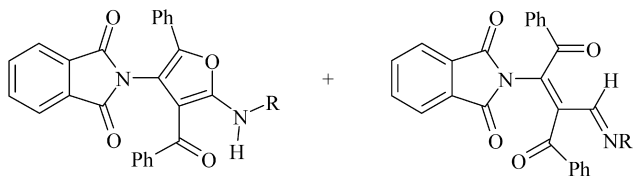

2 **3**

1,2,3	R	%Yield of 2	%Yield of 3
a	*t*-Bu	60	38
b	*c*-Hexyl	60	35

Scheme 1.

^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Partial assignments of the NMR chemical shifts are given in Section 1.

On the basis of the well-established chemistry of isocyanides[4–8] it is reasonable to assume that diaminofurans **2** and imines **3** result from nucleophilic addition of alkyl isocyanides to dibenzoylacetylene and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion **4** is attacked by the anion of the NH-acid to produce the keteneimine **5**, which cyclizes, under the reaction condition employed, to produce the aminofuran **2**,

Keywords: alkyl isocyanides; dibenzoylacetylene; keteneimine; 4-methyl-5-nitroimidazole; phthalimide; saccharin.
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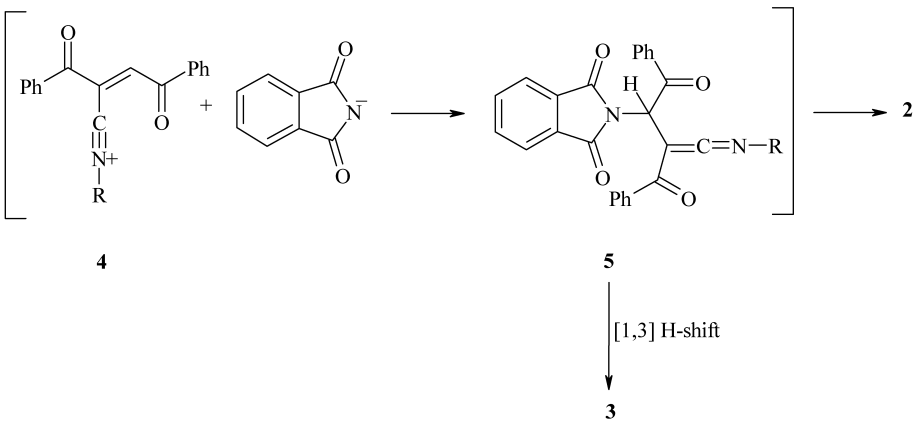
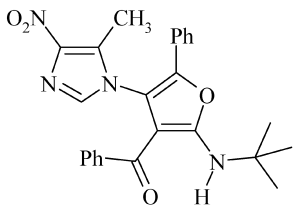


Scheme 2.

or undergoes 1,3-hydrogen shift to produce the imine derivative **3** (Scheme 2).

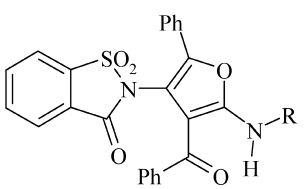
Under the reaction conditions given for phthalimide, only one product was isolated from the reaction mixture of 4-methyl-5-nitroimidazole, *tert*-butyl isocyanide and dibenzoylacetylene. Structure **2c** was assigned to the isolated product on the basis of its elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **2c** showed (besides signals for the phenyl groups) four signals for *tert*-butyl, methyl, methine, and NH protons. The ^{13}C NMR of this product showed 19 signals in agreement with the suggested structure.



2c

From the reaction of saccharin with dibenzoylacetylene in the presence of *tert*-butyl or cyclohexyl isocyanide, only one product was isolated from the reaction mixtures (Scheme 3). Structures **2d** and **2e** were assigned to the isolated products on the basis of their elemental analyses, mass spectra, and IR, ^{1}H NMR and ^{13}C NMR spectroscopic data.

In summary, we have found a simple and efficient method for the preparation of some functionalized aminofurans of potential interest. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.



2	R	%Yield
d	*t*-Bu	95
e	*c*-Hexyl	90

Scheme 3.

1. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded as KBr discs on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C, NMR spectra were obtained at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. Compounds dibenzoylacetylene,[9,10] 4-methyl-5-nitroimidazole[11] and 2-benzoylimidazole[12] were prepared according to the published procedures. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

1.1. General procedure

To a magnetically stirred solution of dibenzoylacetylene (2 mmol) and the NH-acid compound (2 mmol) in 10 mL dry diethyl ether was added a mixture of alkyl isocyanide (2 mmol) in 5 mL dry diethyl ether at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–ethyl acetate mixture as eluent.

1.1.1. 2-[4-Benzoyl-5-(*tert*-butylamino)-2-phenyl-3-furyl]-1*H*-isoindole-1,3-(2*H*)-dione (2a). Yellow crystals, 0.27 g, yield 60%, mp 227–230°C. IR (KBr) (ν_{max}, cm^{-1}): 3348 (N–H), 1775 and 1714 (CO–N–CO), 1618 (C=O). Anal. calcd for $C_{29}H_{24}N_2O_4$ (464.5): C, 74.99; H, 5.21; N, 6.03%. Found: C, 74.8; H, 5.3; N, 6.0%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.60 (9H, s, CMe_3), 6.72 (t, $^{3}J_{HH}$=7.3 Hz, CH arom), 6.89 (t, $^{3}J_{HH}$=7.5 Hz, 2CH arom), 7.20 (t, $^{3}J_{HH}$=7.6 Hz, CH arom), 7.22 (d, $^{3}J_{HH}$=7.6 Hz, 2CH arom), 7.26 (t, $^{3}J_{HH}$=7.5 Hz, 2CH arom), 7.38 (d, $^{3}J_{HH}$=7.8 Hz, 2CH arom), 7.65 (m, 4CH arom), 8.78 (s, N–H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=29.82 (Me_3C), 52.98 (CMe_3), 97.38 and 110.90 (2C of

furan), 123.40 (2CH[4,7] of C_6H_4), 124.29, 126.07, 127.59, 127.68, 128.51, 128.62, 128.80, 131.68, 134.07, 140.42 ($2C_6H_5$ and C_6H_4), 140.49 (C–O), 162.83 (N–C–O), 166.71 (2C=O), 188.77 (C=O). MS, *m/z* (%): 465 (M^++1, 7), 464 (M^+, 22), 409 (12), 408 (53), 407 (21), 303 (4), 260 (6), 232 (2), 197 (2), 148 (12), 106 (7), 105 (100), 76 (15), 54 (10).

1.1.2. 2-{(*Z*)-1-Benzoyl-2-[(*tert*-butylimino)-methyl]-3-oxo-3-phenyl-1-propenyl}-1*H*-isoindole-1,3 (2*H*)-dione (3a). Pale yellow crystals, 0.17 g, yield 38%, mp 169–171°C. IR (KBr) (ν_{max}, cm^{-1}): 1771 and 1704 (CO–N–CO), 1679 (C=O), 1651 (C=N), 1616 (C=C). Anal. calcd for $C_{29}H_{24}N_2O_4$ (464.5): C, 74.99; H, 5.21; N, 6.03%. Found: C, 74.6; H, 5.1; N, 6.0%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.90 (9H, s, Me_3C), 7.12 (s, N=CH), 7.35 (t, $^3J_{HH}$=7.5 Hz, 2CH arom), 7.44–7.53 (m, 4CH arom), 7.75 (d, $^3J_{HH}$=7.6 Hz, 2CH arom), 7.85 (m, 2CH arom), 7.98 (m, 2CH arom), 8.06 (d, $^3J_{HH}$=7.50 Hz, 2CH arom). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=29.29 (Me_3C), 59.19 (CMe_3), 124.44 (2CH arom), 127.59 (C_2 of propenyl), 128.32, 128.60, 128.67, 128.94, 131.55, 132.73, 133.64, 135.16, 136.52, 136.67 ($2C_6H_5$ and C_6H_4), 138.22 (C_1 of propenyl), 152.00 (C=N), 166.00 (2C=O), 189.30 and 194.05 (2C=O). MS, *m/z* (%): 464 (M^+, 2), 333 (7), 318 (20), 278 (8), 277 (31), 230 (6), 148 (10), 147 (43), 129 (13), 105 (100), 83 (13), 76 (18), 75 (11).

1.1.3. 2-[4-Benzoyl-5-(cyclohexylamino)-2-phenyl-3-furyl]-1*H*-isoindole-1,3-(2*H*)-dione (2b). Yellow powder, 0.29 g, yield 60%, mp 238–243°C. IR (KBr) (ν_{max}, cm^{-1}): 3340 (N–H), 1770 and 1710 (CO–N–CO), 1632 (C=O). Anal. calcd for $C_{31}H_{26}N_2O_4$ (490.5): C, 75.90; H, 5.34; N, 5.71%. Found: C, 75.9; H, 5.3; N, 5.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.46–2.14 (m, $5CH_2$ of cyclohexyl), 3.91 (1H, m, CH of cyclohexyl), 6.73 (t, $^3J_{HH}$=7.1 Hz, CH arom), 6.89 (t, $^3J_{HH}$=7.3 Hz, 2CH arom), 7.19–7.28 (m, 5CH arom), 7.38 (d, $^3J_{HH}$=7.3 Hz, 2CH arom), 7.65 (s, 4CH arom), 8.46 (d, $^3J_{HH}$=6.7 Hz N–H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=24.52 ($2CH_2$), 25.40 (CH_2), 33.30 ($2CH_2$), 51.12 (N–CH), 96.79 and 111.06 (2C of furan), 123.39, 124.45, 126.05, 127.58, 127.72, 128.49, 128.60, 128.71, 131.72, 134.01, 140.21 ($2C_6H_5$ and C_6H_4), 140.54 (C–O), 162.53 (N–C–O), 166.72 (2C=O), 188.73 (C=O). MS, *m/z* (%): 491 (M^++1, 15), 490 (M^+, 45), 489 (2), 409 (16), 408 (39), 407 (25), 357 (11), 303 (14), 200 (14), 172 (10), 148 (21), 129 (15), 106 (23), 105 (100), 82 (16), 76 (79), 52 (26).

1.1.4. 2-{(*Z*)-1-Benzoyl-2-[(cyclohexylimino)methyl]-3-oxo-3-phenyl-1-propenyl}-1*H*-isoindole-1,3-(2*H*)dione (3b). Pale yellow crystals, 0.17 g, yield 35%, mp 157–159°C. IR (KBr) (ν_{max}, cm^{-1}): 1770 and 1705 (OC–N–CO), 1681 (C=O), 1654 (C=O), 1600 (C=C), 1588 (C=N). Anal. calcd for $C_{31}H_{26}N_2O_4$ (490.5): C, 75.90; H, 5.34; N, 5.71%. Found: C, 75.6; H, 5.4; N, 5.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.10–1.33 (m, $5CH_2$), 3.26 (m, N–CH), 7.22 (s, N=CH), 7.37 (t, $^3J_{HH}$=7.4 Hz, 2CH arom), 7.45 (t, $^3J_{HH}$=7.4 Hz, 2CH arom), 7.50 (t, $^3J_{HH}$=8.2 Hz, CH arom), 7.52 (t, $^3J_{HH}$=8.2 Hz, CH arom), 7.78 (d, $^3J_{HH}$=7.7 Hz, 2CH arom), 7.86 (m, 2CH arom), 7.98 (m, 2CH arom), 8.08 (d, $^3J_{HH}$=7.5 Hz, 2CH arom). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=23.28, 25.38 and 32.55 ($5CH_2$ of cyclohexyl), 61.79 (N–CH), 124.20 and 128.35 (2CH arom), (128.48 C_2 of propenyl), 120.66, 129.03, 131.23, 132.89, 133.64, 135.14, 136.37, 136.69, 141.54 ($2C_6H_5$ and C_6H_4), (C_1 of propenyl), 150.75 (N=CH), 165.87 (2C=O), 189.15 and 193.84 (2C=O). MS, *m/z* (%): 491 (M^++1, 14), 490 (M^+, 37), 408 (24), 385 (18), 304 (16), 303 (59), 263 (100), 246 (60), 219 (19), 205 (9), 147 (10), 130 (16), 105 (100), 76 (11).

1.1.5. [2-(*tert*-Butylamino)-4-(4-methyl-5-nitro-1*H*-imidazol-1-yl)-5-phenyl-3-furyl]-phenyl) methanone (2c). Yellow powder, 0.42 g, yield 95%, mp 163–167°C. IR (KBr) (ν_{max}, cm^{-1}): 3265 (N–H), 1618 (C=O), 1549 (C=N), 1490 and 1353 (NO_2). Anal. calcd for $C_{25}H_{24}N_4O_4$ (444.5): C, 67.55; H, 5.44; N, 12.60%. Found: C, 67.5; H, 5.5; N, 12.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.62 (s, Me_3C), 2.17 (s, N–CH_3), 6.98 (d, $^3J_{HH}$=8.1 Hz, 2CH arom), 7.07 (d, $^3J_{HH}$=7.7 Hz, 2CH arom), 7.13 (t, $^3J_{HH}$=7.4 Hz, 2CH arom), 7.20 (s, N=CH–N), 7.21–7.30 (m, 4CH arom), 8.94 (s, N–H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=10.70 (N–CH_3), 29.70 (Me_3C), 53.43 (CMe_3), 97.21 and, 113.55 (2C of furan), 123.61 and, 125.44 (4CH of C_6H_5), 127.07 (N–C=N), 127.93, 128.56, 129.35, 130.30, 131.46 ($2C_6H_5$), 134.77 (C^2H of imidazole), 138.98 (C_6H_5), 139.03 and 144.77 (C_4 and C_5 of imidazole), 162.83 (N–C–O), 188.42 (C=O). MS, *m/z* (%): 445 (M^++1, 4), 444 (M^+, 18), 388 (34), 353 (11), 337 (23), 328 (13), 283 (53), 204 (33), 183 (25), 128 (13), 106 (6), 105 (100), 76 (49), 54 (5).

1.1.6. 2-[4-Benzoyl-5-(*tert*-butylamino)-2-phenyl-3-furyl]-1*H*-1,2-benzisothiazole-1,1,3 (2*H*)-trione (2d). Yellow needles, 0.47 g, yield 95%, mp 273–275°C. IR (KBr) (ν_{max}, cm^{-1}): 3235 (N–H), 1738 (C=O), 1621 (C=O), 1365 and 1184 (SO_2). Anal. calcd for $C_{28}H_{24}N_2O_5S$ (500.6): C, 67.18; H, 4.83; N, 5.60%. Found: C, 67.2; H, 4.9; N, 5.6%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.58 (9H, s, CMe_3), 6.90 (t, $^3J_{HH}$=6.2 Hz, CH arom), 7.00 (t, $^3J_{HH}$=6.1 Hz, 2CH arom), 7.23 (t, $^3J_{HH}$=5.8 Hz, CH arom), 7.29 (t, $^3J_{HH}$=6.4 Hz, 2CH arom), 7.40 (d, $^3J_{HH}$=6.4 Hz, 2CH arom), 7.56 (d, $^3J_{HH}$=6.7 Hz, 2CH arom), 7.66 (s, CH arom), 7.76 (s, 2CH arom), 7.98 (s, CH arom), 8.68 (s, N–H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=29.83 (Me_3C), 53.01 (CMe_3), 97.54 and 106.54 (C_4 and C_3 of furan), 120.92, 125.02, 125.32, 126.74, 127.20, 127.32, 127.94, 128.40, 128.73, 129.41, 134.04, 134.89, 137.61 ($2C_6H_5$ and C_6H_4), 140.41 (C–O), 143.27 (C_6H_4), 158.70 (N–C–O), 163.02 (C=O), 189.33 (C=O). MS, *m/z* (%): 500 (M^+, 7), 445 (6), 444 (24), 443 (21), 276 (4), 275 (18), 247 (2), 197 (3), 169 (4), 106 (6), 105 (100), 76 (20), 54 (6).

1.1.7. 2-[4-Benzoyl-5-(cyclohexylamino)-2-phenyl-3-furyl]-1*H*-1,2-benzisothiazole-1,1,3 (2*H*)-trione (2e). Orange powder, 0.47 g, yield 90%, mp 237–240°C. IR (KBr) (ν_{max}, cm^{-1}): 3285 (N–H), 1731 (N–C=O), 1633 (C=O), 1333 and 1185 (SO_2). Anal. calcd for $C_{30}H_{26}N_2O_5S$ (526.6): C, 68.42; H, 4.98; N, 5.32%. Found: C, 68.5; H, 5.1; N, 5.3%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.1–2.16 ($5CH_2$ of cyclohexyl), 3.90 (m, N–CH), 6.92 (t, $^3J_{HH}$=7.3 Hz, CH arom), 7.00 (t, $^3J_{HH}$=7.5 Hz, 2CH arom), 7.24 (t, $^3J_{HH}$=6.8 Hz, CH arom), 7.30 (t, $^3J_{HH}$=7.5 Hz, 2CH arom), 7.42 (t, $^3J_{HH}$=7.6 Hz, 2CH arom), 7.56 (d, $^3J_{HH}$=7.9 Hz, 2CH

arom), 7.68 (m, CH arom), 7.78 (m, 2CH arom), 7.99 (m, CH arom), 8.34 (s, N–H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=24.47 (CH_2), 25.39 ($2CH_2$), 33.27 (CH_2), 33.31 (CH_2), 51.12 (CH), 96.87 and 106.76 (C_4 and C_3 of furan), 120.94, 125.18, 125.32, 126.79, 127.23, 127.28, 127.93, 128.43, 128.64, 129.40, 134.01, 134.84, 137.65 ($2C_6H_5$ and C_6H_4), 140.45 (C–O), 143.05 (C_6H_4), 158.73 (N–C–O), 162.00 (C=O), 189.22 (C=O). MS, *m/z* (%): 527 (M^++1, 7), 526 (M^+, 17), 525 (M^+−1, 2), 444 (7), 443 (7), 370 (12), 289 (11), 288 (45), 287 (53), 275 (32), 106 (18), 105 (100), 82 (27), 76 (61), 52 (54).

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