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Efficient synthesis of functionalized hydrofurans and pyrrolsemploying hexachloroacetone

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Abstract: Isocyanides react smoothly with dimethyl acetylenedicarboxylate in the presence of hexachloroacetone to produce dimethyl 5-[alkyl(aryl)imino]-2,2-bis(trichloromethyl)-2,5-dihydro-furan-3,4-dicarboxylates in high yields. When the reaction was performed in the presence of dibenzoylacetylene, 3-benzoyl-1-alkyl-4-chloro-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-ones were obtained.

Keywords:three-component reaction; isocyanide; hexachloroacetone; iminofurane; activated acetylenes, 2H-pyrrol-2-one, 2,5-dihydrofuran.

Introduction

Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity the isocyanide group differs fundamentally from other functional groups [1]. A classic theme in the chemistry of isocyanides is heterocyclic synthesis [2]. Multi-component reactions (*MCR*s), by virtue of their convergence, facile execution, and generally high yields of products, have attracted much attention from the point of combinatorial chemistry. Of pivotal importance in this area are the isocyanide based *MCR*s such as theversatile *Ugi* and *Passerini* reactions [1-2]. *MCR*s have been used to create diversity oriented and biased combinatorial libraries, to accomplish the synthesis of highly complex natural products.

Results and discution

The reactivity of nucleophilic carbenes such as isocyanides towards dimethyl acetylene dicarboxylate (DMAD)is wellrecognized [3].

The initially formed zwitterionic intermediate, from *DMAD* and an isocyanide, has been shown to undergo further reaction with different electrophilic reagents, leading to a variety of complex heterocycles. These reactions have been the subject of detailed investigation by a number of research groups [1-6]. As part of our current studies on the development of new routes in heterocyclic systems [7], we describe a simple synthesis of trichloromethylatediminofuranes and pyrrol-2-ones by reaction of isocyanides with activated acetylenes in the presence of hexachoroacetone (*HCA*) [8]. Thus, *tert*-butyl isocyanide (**1a)** and *DMAD* undergo a smooth reaction in the presence of *HCA* in dry CH_2Cl_2 at room temperature to produce dimethyl 5-(*tert*-butylimino)-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (**2a)** in 95% yield (Scheme 1) [9]. The structures of compounds **2a**-**2e** were deduced from their

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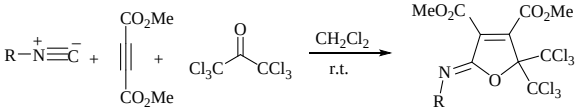
elemental analyses and their IR, ^{1}H-NMR and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values.



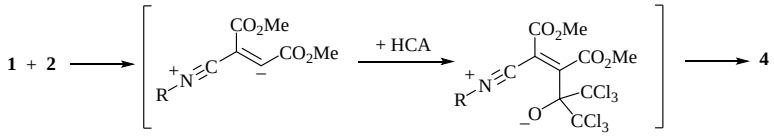
1 **2** **3** **4**

4	R	Yield (%) of **4**
a	t-Bu	95
b	Cyclohexyl	65
c	2,6-Dimethylphenyl	90
d	1,1,3,3-Tetramethylbutyl	80
e	CH_2CO_2Et	75

Scheme 1: Synthesis of iminofurane**4**

The ^{1}H NMR spectrum of **4a** in $CDCl_3$ shows three singlets for tert-butyl (δ = 1.39) and methoxy (δ = 3.85 and 3.90 ppm) protons. The ^{13}C NMR spectrum of **4a**exhibitestowelve signals in agreement with the proposed structure.Partial assignments of these resonances are given in the Experimental section. The ^{1}H NMR and ^{13}C NMR spectra of **4b-4e** are similar to those for 2a except for the alkylimino moieties, which show characteristic resonances in appropriate regions of the spectrum.

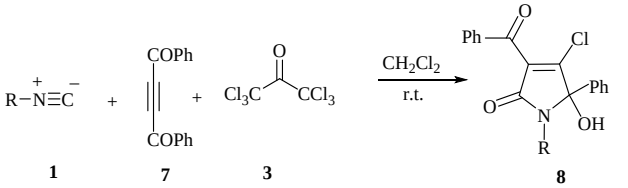
A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that, the initial event is the formation of 1,3-dipolar intermediate **5** from the isocyanide and DMAD [3], which is subsequently attacked by HCA to produce **6**. Intermediate **6** undergoes cyclization reaction to generate **4**.



5 **6**

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

The reaction of alkyl isocyanides with dibenzoylacetylene (*DBA*) [10] in the presence of HCA in CH_2Cl_2 at room temperature led to 3-benzoyl-1-(*tert*-butyl)-4-chloro-5-hydroxy-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-ones **5** (Scheme 3)[11] The ^{1}H NMR spectrum of **5a** showed two singlets arising from *tert*-butyl (δ = 1.29 ppm) and hydroxy (δ = 6.14 ppm) protons, along with the aromatic protons. The^{13}C NMR spectrum of **5a** shows fifteen distinct resonances in agreement with the proposed structure.

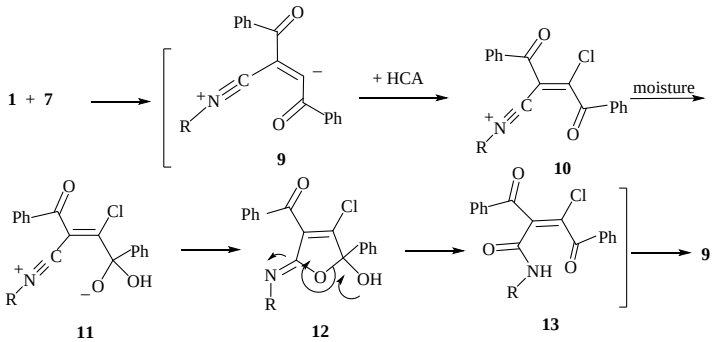


1 **7** **3** **8**

8	R	Yield (%) of **8**
a	^{t}-Bu	95
b	1,1,3,3-Tetramethylbutyl	90

Scheme 3. Synthesis of pyrrole derivatives **8**

A plausible mechanism for the formation of **8** is proposed in Scheme 4. The initial event is the formation of 1,3-dipolar intermediate **9** from the isocyanide and DBA which is subsequently attacked by HCA to produce **10**[8] In the presence of moisture, intermediate **10** is transformed to**11**, which undergoes cyclization reaction to generate **12**. Intermediate **12**, rearranges to **13**, via the open-chain structure **13**.



Scheme 4: Proposed mechanism for the synthesis of **9**

In conclusion, we described a convenient route to bis-trichloromethylated iminofuranes, from isocyanides and DMAD in the presence of HCA. The functionalized iminofuranes, reported in this work may be considered as potentially useful synthetic intermediates. When the reaction was performed in the presence of DBA, functionalized pyrrol-2-ones were obtained. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of functionalized iminofuranes and pyrrol-2-ones.

Experimental

Dibenzoylacetylene was prepared according to Ref. [9]. 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.

General Procedure for the Preparation of 2,5-dihydrofurans 4

To a stirred solution of DMAD**2** (0.28 g, 2 mmol) and of HCA**3**(0.52 g, 2 mmol) in CH_2Cl_2 (10 cm^3) was added the alkyl(aryl) isocyanide**1**(2 mmol) at room temperature. The reaction mixture was then stirred for 24 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 hexane-EtOAc as eluent to give product.

Dimethyl 5-(tert-butylimino)-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (4a)

Colerless crystals, m.p. 141-144°C; yield: 0.80 g, 95%. IR (KBr): ν = 1736, 1698, 1427, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.39 (s, CMe_3), 3.85 (s, MeO), 3.90 (s, MeO) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):*δ* = 29.4 (C*Me*$_3$), 53.1 (OMe), 53.2 (OMe), 56.2 (C-N), 98.0 (2 CCl_3), 99.7 (C-O), 141.2 and 142.0 (2 C), 147.7 (C=N), 160.6 and 160.7 (2 C=O) ppm; MS (EI, 70 Ev): *m*/*z* (%) = 489 ($M^{+\bullet}$, 2), 474 (25), 320 (40), 260 (25), 58 (100), 41(50).

Dimethyl 5-(cyclohexlimino)-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate(4b)

Yellow oil; yield0.66 g, 65%; IR (KBr): ν = 1734, 1690, 1420, 1273 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.25 (m, 2 CH_2), 1.27 (m, 2 CH_2), 1.31 (m, CH_2), 3.62 (m, N-CH), 3.64 (s,

OMe), 3.77 (s, OMe) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):δ= 24.5 (CH_2), 24.7 (2 CH_2), 25.7 (2 CH_2), 51.2 and 53.1 (2 OMe), 53.8 (C-N), 95.0 (2 CCl_3), 99.8 (C-O), 134.5 and 135.3 (2 C), 159.5 (C=N), 160.9 and 161.2 (2 C=O) ppm.

Dimethyl 5-[(2,6-dimethylphenyl)imino]-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (4c)

Yellow powder, m.p. 140-142°C; yield 0.96 g, 90%;IR (KBr): ν = 1737, 1715, 1426, 1276 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ= 2.22 (s, 2 CH_3), 3.97 (s, OMe), 4.03 (s, OMe), 6.99 (t, $^3J_{HH}$ = 6.9 Hz, CH), 7.07 (t, $^3J_{HH}$ = 7.5 Hz, 2 CH) ppm;^{13}C NMR (125.7 MHz, $CDCl_3$):δ= 18.5 (2 Me), 53.8 and 53.9 (2 OMe), 97.7 (2 CCl_3), 100.1 (C-O), 124.6 (CH), 127.4 (2 C), 128.0 (2 CH), 141.5, 143.0,145.7 (3 C), 147.0 (C=N), 160.5 and 160.8 (2 C=O) ppm; MS (EI, 70 Ev): *m*/*z*(%) = 538 (M^+, 30), 537 (42), 420 (88), 418 (100), 121(42), 119 (100), 117(90).

Dimethyl 5-[(1,1,3,3-tetrabuthyl)imino]-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (4d)

Yellow oil; yield 0.92 g, 80%;IR (KBr): ν = 1742, 1736, 1430, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.00 (s, CMe_3), 1.47 (s, 2 CH_3), 1.55 (s, CH_2), 3.89 (s, OMe), 3.95 (s, OMe) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):δ = 29.9 (2 CH_3), 31.9 (CMe_3), 32.3 (C), 53.5 and 53.6 (2 OMe), 55.9 (CH_2), 60.1 (C-N), 98.5 (2 CCl_3), 99.9 (C-O), 141.7 and 142.2 (2 C), 147.1 (C=N), 161.0 and 161.2 (2 C=O) ppm; MS (EI, 70 Ev): *m*/*z* (%) = 474 (25), 395 (20), 322 (20), 121 (18), 119 (62), 117 (100), 57 (30).

Dimethyl 5-[(2-ethoxy-2-oxo)imino]-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (4e).

Red oil; yield 0.76 g, 75%;IR (KBr): ν = 1740,1736,1429, 1271 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.29 (t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.89 (s, OMe), 3.96 (s, OMe), 4.24 (q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.41 (s, CH_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):δ = 14.6 (CH_3), 51.0 (C-N), 53.8 and 53.9 (2 OMe), 61.7 (OCH_2), 98.0 (2 CCl_3), 99.8 (C-O), 138.4 and 146.4 (2 C), 155.3 (C=N), 160.1, 160.7 and 168.9 (3 C=O) ppm; MS (EI, 70 Ev): *m*/*z* (%) = 519 (M^+, 2), 368 (60), 317 (60), 121 (80), 119 (100), 117 (100), 59 (40).

General Procedure for the Preparation of 1,5-dihydro-2H-pyrrol-2-ones 9

To a stirred solution of DBA**7**(0.48 g, 2 mmol) and HCA **3**(0.52 g, 2 mmol) in CH_2Cl_2 (10 cm^3) was added the alkyl(aryl) isocyanide**1**(2 mmol)at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by precipitation in Et_2O to give **9**.

3-Benzoyl-1-(tert-butyl)-4-chloro-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (9a, $C_{21}H_{20}Cl_6NO_3$)

Pale yellow powder, m.p. 139-142°C; yield: 0.68 g, 92%; IR (KBr): ν = 3390, 1672, 1604, 1367 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.29 (s, CMe_3), 6.14 (s, OH), 7.23 (t, $^3J_{HH}$ = 7.7 Hz, CH), 7.26 (d, $^3J_{HH}$ = 7.6 Hz, CH), 7.34 (m, 3 CH), 7.45 (d, $^3J_{HH}$ = 7.3 Hz, CH), 7.50 (t, $^3J_{HH}$ = 7.7 Hz, 2 CH), 7.64 (d, $^3J_{HH}$ = 7.2 Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):δ = 28.8 (CMe_3), 52.2 (C), 90.2 (C-O), 124.9 (2 CH), 125.6 (C), 127.7 (2 CH), 128.0 (2 CH), 129.0 (2 CH), 129.2 (CH), 130.0 (CH), 133.4 and 135.5 (2 C), 140.7 (C-Cl), 170.5 and 179.9 (2 C=O) ppm; MS (EI, 70 Ev): *m*/*z* (%) = 278 (10), 117 (20), 105 (66), 77 (40), 58 (100), 42 (40).

3-Benzoyl-4-chloro-5-hydroxy-5-phenyl -1-(1,1,3,3-tetramethylbutyl)-1,5-dihydro-2H-pyrrol-2-one (9b).

Pale yellow powder, m.p. 126-129°C, yield 0.80 g, 85%; IR (KBr): ν = 3380, 1667, 1606 ,1364 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): □ = 0.98 (s, CMe_3), 1.05 (s, CH_3), 1.36 (s, CH_3), 1.85 (AB system, J_{AB} = 15 Hz, CH_2), 6.10 (s, OH), 7.22 (t, $^3J_{HH}$ = 8.2 Hz, CH), 7.31 (d, $^3J_{HH}$ = 8.8 Hz, CH), 7.44 (t, $^3J_{HH}$ = 7.2 Hz, CH), 7.50 (m, 4 CH), 7.64 (d, $^3J_{HH}$ = 7.3 Hz, 2 CH), 8.01 (d, $^3J_{HH}$ = 7.3 Hz, CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$):δ = 28.5 (CH_3), 31.8 (CMe_3), 31.9 (C), 32.0 (CH_3), 51.3 (C), 56.8 (CH_2), 90.6 (C-O), 125.4 (2 CH), 126.1 (C), 128.1 (2 CH), 128.4 (2 CH), 129.2 (2 CH), 129.6 (CH), 130.4 (CH), 134.1 (C), 136.9 (C), 141.3 (C-Cl), 171.2 and 180.5 (2 C=O) ppm; MS (EI, 70 Ev): *m*/*z* (%) = 320 (5), 119 (64), 117 (66), 84 (86), 82 (90), 58 (14), 48 (100).

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