Monatsh Chem 139, 625–628 (2008)
DOI 10.1007/s00706-007-0810-3
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Efficient synthesis of functionalized 2,5-dihydrofurans and 1,5-dihydro-2*H*-pyrrol-2-ones by reaction of isocyanides with activated acetylenes in the presence of hexachloroacetone

Issa Yavari, Maryam Sabbaghan, Zinatossadat Hossaini

Chemistry Department, Tarbiat Modares University, Tehran, Iran

Received 19 August 2007; Accepted 20 September 2007; Published online 29 April 2008

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 with dibenzoylacetylene, 3-benzoyl-1-alkyl-4-chloro-5-hydroxy-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-ones were obtained.

Keywords Three-component reaction; Isocyanide; Hexachloroacetone; Iminofurane; 2,5-Dihydrofurans.

Introduction

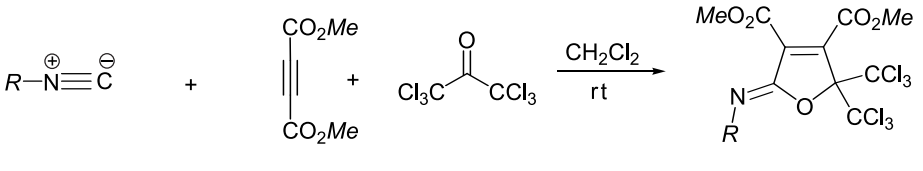
Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity the isocyanide group differs fundamentally from other functional groups [1]. A classic theme in the chemistry of isocyanides is heterocyclic synthesis [2]. Multi-component reactions (MCRs), 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 MCRs such as the versatile *Ugi* and *Passerini* reactions [1, 2]. MCRs have been used to create diversity oriented and biased combinatorial compound assemblies, to accomplish the synthesis of highly complex natural products.

Correspondence: Issa Yavari, Chemistry Department, Tarbiat Modares University, Tehran, Iran. E-mail: yavarisa@modares.ac.ir

Results and discussion

The reactivity of nucleophilic carbenes such as isocyanides towards dimethyl acetylenedicarboxylate (*DMAD*) is well recognized [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 trichloromethylated iminofuranes 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 **2a**–**2e** were deduced from 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.

The ^{1}H NMR spectrum of **2a** in $CDCl_3$ shows three singlets for *tert*-butyl ($\delta = 1.39$ ppm) and me-

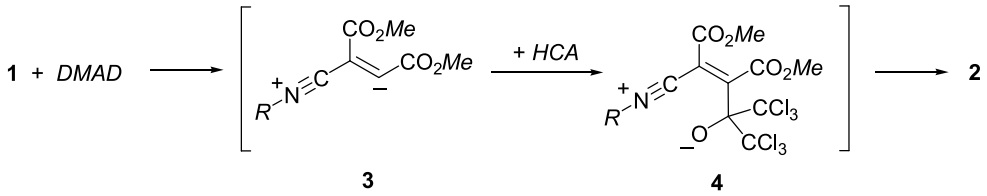


R — DMAD — HCA — R

1a *t*Bu
1b Cyclohexy
1c 2,6-Dimethylphenyl
1d 1,1,3,3-Tetramethylbutyl
1e CH_2CO_2Et

2a *t*Bu
2b Cyclohexy
2c 2,6-Dimethylphenyl
2d 1,1,3,3-Tetramethylbutyl
2e CH_2CO_2Et

Scheme 1



3 **4**

Scheme 2

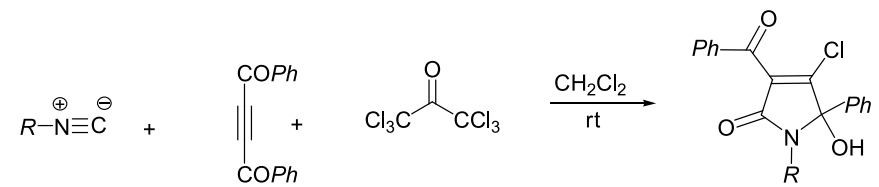
thoxy ($\delta = 3.85$ and 3.90 ppm) protons. The ^{13}C NMR spectrum of **2a** exhibites twelve signals in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section. The ^{1}H NMR and ^{13}C NMR spectra of **2b**–**2e** are similar to those 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 **3** from the isocyanide and *DMAD* [3], which is subsequently attacked by *HCA* to produce **4**. Intermediate **4** undergoes cyclization reaction to generate **2**.

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 ($\delta = 1.29$ ppm) and hydroxy ($\delta = 6.14$ ppm) protons, along with the aromatic protons. The ^{13}C NMR spectrum of **5a** shows fifteen distinct resonances in agreement with the proposed structure.

A plausible mechanism for the formation of **5** is proposed in Scheme 4. The initial event is the formation of 1,3-dipolar intermediate **3** from the isocyanide and *DBA* which is subsequently attacked by *HCA* to produce **7** [8a]. In the presence of moisture, intermediate **7** is transformed to **8**, which undergoes cyclization reaction to generate **9**. Intermediate **9**, rearranges to **5**, *via* the open-chain structure **10**.

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

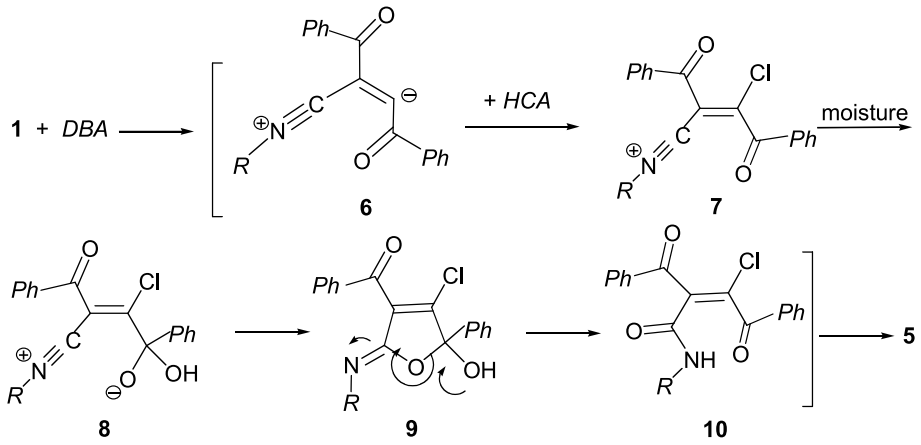


R — DBA — HCA — R

1a *t*Bu
1b 1,1,3,3-Tetramethylbutyl

5a *t*Bu
5b 1,1,3,3-Tetramethylbutyl

Scheme 3



Scheme 4

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-MAT 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 ***2***
To a stirred solution of 0.28 g *DMAD* (2 mmol) and 0.52 g *HCA* (2 mmol) in 10 cm^3 CH_2Cl_2 was added 2 mmol of the alkyl(aryl) isocyanide 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 *n*-hexane-*Et*O*Ac* as eluent to give the product.

Dimethyl 5-(tert-butylimino)-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (**2a**, $C_{14}H_{15}Cl_6NO_5$)
Colorless crystals, mp 141–144°C; yield 0.80 g (95%); IR (KBr): $\bar{\nu} = 1736$, 1698, 1427, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.39$ (s, C*Me*$_3$), 3.85 (s, *Me*O), 3.90 (s, *Me*O) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 29.4$ (C*Me*$_3$), 53.1 (O*Me*), 53.2 (O*Me*), 56.2 (C–N), 98.0 ($2CCl_3$), 99.7 (C–O), 141.2, 142.0 (2C), 147.7 (C=N), 160.6, 160.7 (2C=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 (**2b**, $C_{16}H_{17}Cl_6NO_5$)
Yellow oil, yield 0.66 g (65%); IR (KBr): $\bar{\nu} = 1734$, 1690, 1420, 1273 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.25$ (m, $2CH_2$), 1.27 (m, $2CH_2$), 1.31 (m, CH_2), 3.62 (m, N–CH), 3.64 (s, O*Me*), 3.77 (s, O*Me*) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 24.5$ (CH_2), 24.7 ($2CH_2$), 25.7 ($2CH_2$), 51.2, 53.1 (2O*Me*), 53.8 (C–N), 95.0 ($2CCl_3$), 99.8 (C–O), 134.5, 135.3 (2C), 159.5 (C=N), 160.9, 161.2 (2C=O) ppm.

Dimethyl 5-[(2,6-dimethylphenyl)imino]-2,2-bis(trichloromethyl)-2,5-dihydrofuran-3,4-dicarboxylate
(**2c**, $C_{18}H_{15}Cl_6NO_5$)
Yellow powder, mp 140–142°C; yield 0.96 g (90%); IR (KBr): $\bar{\nu} = 1737, 1715, 1426, 1276$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.22$ (s, $2CH_3$), 3.97 (s, O*Me*), 4.03 (s, O*Me*), 6.99 (t, $^3J_{HH} = 6.9$ Hz, CH), 7.07 (t, $^3J_{HH} = 7.5$ Hz, 2CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 18.5$ (2*Me*), 53.8, 53.9 (2O*Me*), 97.7 ($2CCl_3$), 100.1 (C–O), 124.6 (CH), 127.4 (2C), 128.0 (2CH), 141.5, 143.0,145.7 (3C), 147.0 (C=N), 160.5, 160.8 (2C=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 (**2d**, $C_{18}H_{23}Cl_6NO_5$)
Yellow oil, yield 0.92 g (80%); IR (KBr): $\bar{\nu} = 1742$, 1736, 1430, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (s, C*Me*$_3$), 1.47 (s, $2CH_3$), 1.55 (s, CH_2), 3.89 (s, O*Me*), 3.95 (s, O*Me*) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 29.9$ ($2CH_3$), 31.9 (C*Me*$_3$), 32.3 (C), 53.5, 53.6 (2O*Me*), 55.9 (CH_2), 60.1 (C–N), 98.5 ($2CCl_3$), 99.9 (C–O), 141.7, 142.2 (2C), 147.1 (C=N), 161.0, 161.2 (2C=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 (**2e**, $C_{14}H_{13}Cl_6NO_7$)
Red oil, yield 0.76 g (75%); IR (KBr): $\bar{\nu} = 1740, 1736, 1429, 1271\,cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.29$ (t, $^3J_{HH} = 7.1$ Hz, CH_3), 3.89 (s, O*Me*), 3.96 (s, O*Me*), 4.24 (q, $^3J_{HH} = 7.1$ Hz, OCH_2), 4.41 (s, CH_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.6$ (CH_3), 51.0 (C–N), 53.8, 53.9 (2O*Me*), 61.7 (OCH_2), 98.0 ($2CCl_3$), 99.8 (C–O), 138.4, 146.4 (2C), 155.3 (C=N), 160.1, 160.7, 168.9 (3C=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 ***5***
To a stirred solution of 0.48 g *DBA* (2 mmol) and 0.52 g *HCA* (2 mmol) in 10 cm^3 CH_2Cl_2 was added 2 mmol alkyl(aryl) isocyanide 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 **5**.

3-Benzoyl-1-(tert-butyl)-4-chloro-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (**5a**, $C_{21}H_{20}Cl_6NO_3$)
Pale yellow powder, mp 139–142°C; yield 0.68 g (92%); IR (KBr): $\bar{\nu} = 3390, 1672, 1604, 1367\,cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.29$ (s, C*Me*$_3$), 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, 3CH), 7.45 (d, $^3J_{HH} = 7.3$ Hz, CH), 7.50 (t, $^3J_{HH} = 7.7$ Hz, 2CH), 7.64 (d, $^3J_{HH} = 7.2$ Hz, 2CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 28.8$ (C*Me*$_3$), 52.2 (C), 90.2 (C–O), 124.9 (2CH), 125.6 (C), 127.7 (2CH), 128.0 (2CH), 129.0 (2CH), 129.2 (CH), 130.0 (CH), 133.4, 135.5 (2C), 140.7 (C–Cl), 170.5, 179.9 (2C=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 (**5b**, $C_{25}H_{28}ClNO_3$)
Pale yellow powder, mp 126–129°C; yield 0.80 g (85%); IR (KBr): $\bar{\nu} = 3380, 1667, 1606, 1364\,cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (s, C*Me*$_3$), 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, 4CH), 7.64 (d, $^3J_{HH} = 7.3$ Hz, 2CH), 8.01 (d, $^3J_{HH} = 7.3$ Hz, CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 28.5$ (CH_3), 31.8 (C*Me*$_3$), 31.9 (C), 32.0 (CH_3), 51.3 (C), 56.8 (CH_2), 90.6 (C–O), 125.4 (2CH), 126.1 (C), 128.1 (2CH), 128.4 (2CH), 129.2 (2CH), 129.6 (CH), 130.4 (CH), 134.1 (C), 136.9 (C), 141.3 (C–Cl), 171.2, 180.5 (2C=O) ppm; MS (EI, 70 eV): m/z (%) = 320 (5), 119 (64), 117 (66), 84 (86), 82 (90), 58 (14), 48 (100).

References

1. a) Dömling A, Ugi I (2000) Angew Chem Int Ed Eng 39:3169; b) Dömling A (2006) Chem Rev 106:17
2. Marcaccini S, Torroba T (1993) Org Prep Preced Int 25:141
3. Nair VJ, Rajesh C, Vinod AU, Bindu S, Sreekanth AR, Mathess JS, Balagopal L (2003) Acc Chem Res 36:899
4. Teimouri MB, Shaabani A, Bazhrang R (2006) Tetrahedron 62:1845
5. Esmaeili AA, Zendegani H (2005) Tetrahedron 61:4031
6. Nair V, Vinod AU, Abhilash N, Menon RS, Santhi V, Varma RL, Viji S, Mathew S, Srinivas R (2003) Tetrahedron 59:10279
7. a) Yavari I, Sabbaghan M, Hossaini Z (2006) Synlet:2501; b) Yavari I, Djahaniani H (2006) Tetrahedron Lett 47:2953; c) Yavari I, Moradi L (2006) Tetrahedron Lett 47:1627; d) Yavari I, Djahaniani H (2005) Tetrahedron Lett 46:7491
8. Hexachloroacetone was introduced as a source of positive chlorine: Laskovics FM, Schulman EM (1977) Tetrahedron Lett 18:759 and dichlorocarbene: Grant FW, Cassie WB (1960) J Org Chem 25:1443; Grant FW, Cassie WB (1960) J Org Chem 25:2263, and has been used for the preparation of amides: Panetta CA, Casanova TG (1970) J Org Chem 35:2423 and alkyl trichloroacetates: Freedlander RS, Bryson TA, Dunlap RB, Schulman EM, Lewis CA (1981) J Org Chem 46:3519
9. a) Skattebøl L, Jones ERH, Whiting MC (1963) Org Synth Coll vol 4:792; b) Bowden K, Heilbron IM, Jones ERH, Weedon BC (1946) J Chem Soc:39