The new γ-spiroiminolactone synthesis by reaction between alkyl or aryl isocyanides and 1,10-phenanthroline-5,6-dione in the presence of acetylenic esters

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The 1:1 intermediate generated by the addition of alkyl and aryl isocyanides to dialkyl acetylenedicarboxylate is trapped by 1,2-dicarbonyl compounds such as 1,10-phenanthroline-5,6-dione (phendione) to yield iminolactones in good yields.

Keywords: iminolactone derivatives, isocyanides, acetylenic esters, phendione, three-compnent reactions

Reactions are the tool kits for chemists to create new matter with novel properties and they are the basis for today's organic chemistry art of assembling complex molecules with predefined properties.[1]

Recentely, γ-spirolactones have been the subject of great consideration because of their effects as antibacterial agents, aldostrone inhibitors and proper precursors for the preparation of a wide spectrum of natural compounds.[2] Iminolactones have been hydrolysed with aqueous hydrochloric acid for 2 h producing butenolides,[3] also named furan-2(5*H*)-ones,[1] form an important class of natural products that are biologically active compounds and used in medicine and in agriculture.[4-8]

The reactivity of nucleophilic carbenes such as isocyanides towards dimethyl acetylenedicarboxylate (DMAD) is well documented.[9-11] The reaction of isocyanides with carbon–carbon triple bonds occurs in a stepwise manner through a zwitterionic intermediate, the ultimate fate of which appears to be dictated by the nature of original triple-bonded substrate.[12 15]

The initially formed zwitterionic intermediate has been shown to undergo further reaction with DMAD and isocyanide in different molar proportions, leading to a variety of complex heterocyclic compounds and these reactions have been the subject of detailed investigation by a number of research groups.[16–20]

In order to confirm the presence of highly reactive intermediates derived from isocyanides and acetylenic esters which are then likely to undergo addition to 1,10-phenanthroline-5,6-dione (phendione) leading to heterocycles. We initiated an investigation of the reaction of isocyanides and acetylenic esters with phendione (see Scheme 1).

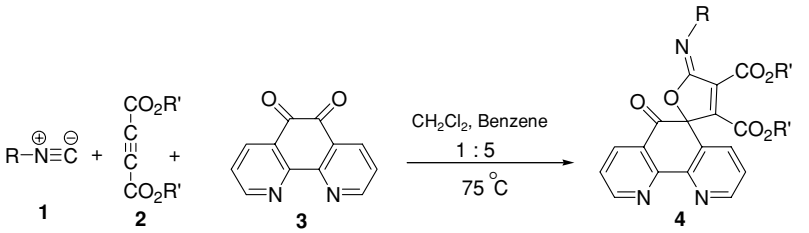
Note that attempts to trap such zwitterionic intermediates with olefinic dipolarophiles such as cyclohexene and dimethyl fumarate have failed.[19] However, the existence of 1:1 intermediate indicated by the isolation of 1:1:1 heterocyclic adducts from the reaction mixture of isocyanide with DMAD in the presence of phendione.

Thus, alkyl and aryl isocyanides (**1**) and acetylenic esters (**2**) in the presence of 1,10-phenanthroline-5,6-dione (phendione) (**3**) undergo a cycloaddition reaction in mixture of dichloromethane and benzene (1:5) at 75 °C to produce γ-spiroiminolactones (**4**) in good yields. On the basis of the well established chemistry of isocyanides,[12, 13] it is reasonable to assume that compounds (**4**) result from addition of alkyl and aryl isocyanides to the acetylenic esters and concomitant addition to phendione leading to γ-spiroiminolactones (Scheme 2).

Structures (**4**) were assigned on the basis of their IR, ^{1}H and ^{13}C NMR as well as mass spectral data. The IR spectrum of (**4a**) showed strong absorptions at 1735, 1725 and 1715 cm^{-1} due to the ester and ketone carbonyl groups, 1691 cm^{-1} due to C=N. The ^{1}H NMR spectrum of (**4a**) exhibited two singlets arising from the *tert*-butoxy groups (δ 0.97 and 1.56).

The ^{13}C NMR spectrum showed 27 distinct resonances consistent with the γ-spiroiminolactone structure (see experimental section). The characteristic signal due to the spiro carbon was described at δ 85.51. The ^{1}H and ^{13}C NMR spectra of (**4a–d**) are similar to those of (**4a**), except for isocyanide, ester residues.

We now report that phendione undergoes a smooth reaction with 2 equiv. of dimethyl acetylenedicarboxylate in the presence of 2 equiv. of *tert*-butyl isocyanide in a mixture of dichloromethane and benzene (1: 5) in 75 °C to produce (**5**) in 92% yield (Scheme 3). A mixture of racemic or *meso* compounds are possible for compound **5**. The *meso* isomer should suffer from sterict crowding of the ester groups, thus



1	R
a	Cyclohexyl
b	2,6-dimethylphenyl
c	2,6-dimethylphenyl
d	2,6-dimethylphenyl

2	R'
a	Me
b	Et
c	*t*-butyl

4	R	R'	% Yield
a	Cyclohexyl	*t*-butyl	93
b	2,6-dimethylphenyl	Me	88
c	2,6-dimethylphenyl	Et	93
d	2,6-dimethylphenyl	*t*-butyl	90

Scheme 1

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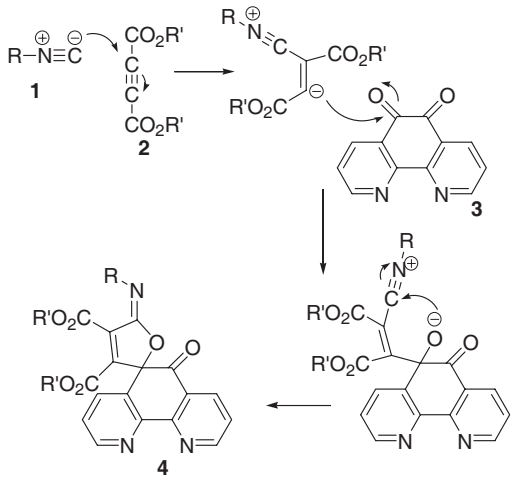


Scheme 2

compound **5** is racemic.[21] This reaction has already been examined by addition 1:1:1 of *tert*-butyl isocyanide, DMAD and phendione and the mixture of monospiro, dispiro and unchanged phendione were obtained.

In conclusion, a three-component condensation reaction is required. It offers an easy and effective one-pot synthesis of iminolactones which are potentially amenable to a number of synthetic transformation.[22]

Experimental

Dialkyl acetylenedicarboxylates, *tert*-butyl, cyclohexyl and 2,6-dimethylphenyl isocyanides were obtained from Fluka (Buchs, Switzerland) and were used without further purification and phendione was prepared from phenanthroline by known methods.[23,24] Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Shimadzu IR-470 spectrometer. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyser. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX – 500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionisation potential of 70 eV.

General procedure

(Examplified by di-*tert*-butyl 5-cyclohexylimino-6'-oxo-5*H*,6*H'*-spiro[furan-2,5'-[1,10]phenanthroline]-3,4-dicarboxylate) (**4a**).

The mixture of phendione (0.21 g, 1 mmol) was dissolved in 5 ml of dry CH_2Cl_2 and was then added to di-*tert*-butyl acetylenedicarboxylate (0.27 g, 1.2 mmol) in 20 ml dry benzene and a mixture of cyclohexyl isocyanide (0.147 ml, 1.2 mmol) in 5 ml of benzene was added dropwise at room temperature over 3 min. Then was allowed to warm up 75 °C for 15 h. After this time was removed the solvent and was washed crystals of product by (2 × 5) ml of cold diethyl ether.

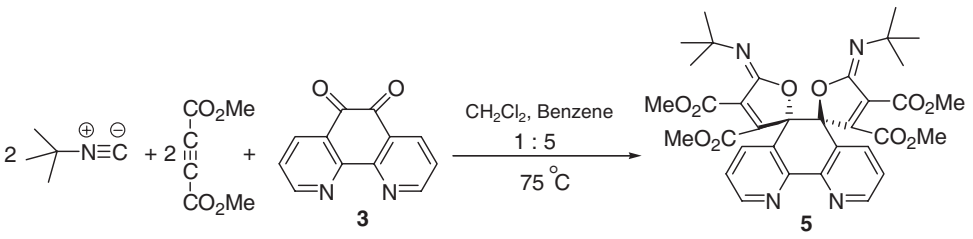
4a: Pale powder. m.p. 191.5–193.5 °C, yield: 0.50 g (93%), IR (KBr) (ν_{max} , cm^{-1}): 1735, 1725 and 1715 (3 C=O), 1691 (C=N). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 0.97 (9H, s, C*Me*$_3$), 1.21–1.77 (10H, m, 5C*H*$_2$), 1.56 (9H, s, C*Me*$_3$), 3.57 (1H, m, C*H*–N), 7.44 (1H, dd, J_1=7.6, J_2=4.5 Hz, C*H*), 7.51 (1H, dd, J_1=7.5, J_2=4.7 Hz, C*H*), 7.68 (1H, d, *J*=8.0 Hz, C*H*), 8.42 (1H, d, *J*=7.7 Hz, C*H*), 8.91 (1H, d, *J*=4.0 Hz, NC*H*), 9.09 (1H, d, *J*=3.5 Hz, NC*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 24.23, 24.27 and 25.70 (3CH_2 of cyclohexyl), 27.32 and 28.06 (2OC*Me*$_3$), 32.97 and 33.16 (2*CH*$_2$ of cyclohexyl), 56.09 (N–CH), 84.02 and 84.13 (2O*C*Me$_3$), 85.51 (C$_{spiro}$), 123.88, 124.78, 125.04, 126.06, 131.49, 134.87, 137.71, 143.74, 148.06, 151.55, 153.64 and 154.00 (C=C$_{iminolactone}$ and C$_{arom}$), 155.96 (C=N), 158.38, 160.02 and 190.16 (3C=O). MS (*m/z*, %): 547 (M$^+$+2, 5), 546 (M$^+$+1, 3), 488 (3), 389 (14), 361 (3), 262 (21), 57 (100), 41 (80). Anal Calcd for $C_{31}H_{35}N_3O_6$ (545.63): C, 68.24; H, 6.47; N, 7.70%; Found: C, 67.75; H, 6.50; N, 7.82%.

4b: Yellow powder. m.p. 194–196 °C, yield: 0.42 g (88%); IR (KBr) (ν_{max}, cm^{-1}): 1747, 1735 and 1720 (3 C=O), 1681 (C=N). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 2.20 (6H, s, Ar–*Me*$_2$), 3.51, 4.03 (6H, 2s, 2O*Me*), 6.86, (1H, t, *J*=7.4 Hz, Ar–*H*), 6.96 (2H, d, *J*=7.4 Hz, Ar–*H*), 7.45 (1H, dd, J_1=7.5, J_2=4.6 Hz, CH), 7.51 (1H, dd, J_1=7.5, J_2=4.6 Hz, CH), 7.67 (1H, d, *J*=7.5 Hz, CH), 8.38 (1H, d, *J*=7.0 Hz, CH), 8.92 (1H, d, *J*=3.6 Hz, NCH), 9.09 (1H, d, *J*=3.2 Hz, NCH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 17.96 (Ar–*Me*$_2$), 53.17 and 53.50 (2O*Me*), 86.88 (C$_{spiro}$), 124.04, 124.94, 124.99, 125.56, 127.13, 127.48, 129.67, 135.35, 135.81, 136.53, 143.32, 144.59, 148.24, 151.98, 153.31 and 154.50 (C=C$_{iminolactone}$ and C$_{arom}$), 156.22 (C=N), 159.39, 160.90 and 188.83 (3C=O). MS (*m/z*, %): 484 (M$^+$+1, 31), 483 (M$^+$, 100), 468 (2), 452 (18), 364 (20), 336 (31), 59 (16). Anal Calcd for $C_{27}H_{21}N_3O_6$ (483.47): C, 67.07; H, 4.38; N, 8.69%; Found: C, 66.80; H, 4.29; N, 8.73%.

4c: Pole powder. m.p. 214.8–217 °C, yield: 0.48 g (93%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1732, 1726 and 1699 (3C=O), 1669 (C=N). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.32 (3H, t, *J*=7.0 Hz, OCH$_2$–*CH*$_3$), 1.35 (3H, t, *J*=7.0 Hz, OCH$_2$-*CH*$_3$), 1.97 (6H, s, Ar–*Me*$_2$), 4.28 (2H, q, *J*=7.0 Hz, O*CH*$_2$), 4.33 (2H, q, J=7.0 Hz, O*CH*$_2$), 6.96 (2H, d, *J*=7.5 Hz, Ar–*H*), 7.02 (1H, dd, J_1=7.9, J_2=5.0 Hz, CH), 7.06 (1H, t, *J*=7.5 Hz, Ar–*H*), 7.47 (1H, dd, J_1=8.0, J_2=5.0 Hz, CH), 7.77 (1H, d, *J*=7.9 Hz, CH), 8.23 (1H, d, *J*=8.0 Hz, CH), 8.38 (1H, d, *J*=5.0 Hz, NCH) 8.47 (1H, d, *J*=5.0 Hz, NCH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 13.89 and 14.22 (2OCH$_2$-*CH*$_3$), 17.99 (Ar–*Me*$_2$), 60.04 and 61.77 (2O*C*H$_2$CH$_3$), 88.45 (C$_{spiro}$), 117.81, 122.93, 123.42, 125.00, 125.56, 126.43, 127.16, 128.35, 133.25, 135.13, 138.09, 138.83, 143.00, 144.31, 150.21 and 155.11(C=C$_{iminolactone}$ and C$_{arom}$), 160.17 (C=N), 164.09, 166.18 and 187.02 (3C=O). MS (*m/z*, %): 512 (M$^+$+1, 7), 511 (M$^+$, 3), 466 (7), 438 (28), 364 (14), 192 (100), 44 (69). Anal Calcd for $C_{29}H_{25}N_3O_6$ (511.17): C, 68.09; H, 4.93; N, 8.21%; Found: C, 68.31; H, 4.95; N, 8.15%.

4d: Brown powder. m.p. 212–215 °C, yield: 0.51 g (90%); IR (KBr) (ν_{max}, cm^{-1}): 1730, 1718 and 1710 (3C=O), 1663 (C=N). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.52 and 1.54 (18H, 2s, 2OC*Me*$_3$), 1.90 (6H, s, Ar–*Me*$_2$), 6.87 (2H, d, *J*=7.0 Hz, Ar–*H*), 6.92 (1H, dd, J_1=7.1, J_2=4.8 Hz, CH), 6.98 (1H, t, *J*=7.0 Hz, Ar–*H*), 7.31 (1H, dd, J_1=7.0, J_2=5.0 Hz, CH), 7.66 (1H, d, *J*=7.5 Hz, CH), 8.01 (1H, d, *J*=8.0 Hz, CH), 8.32 (1H, d, *J*=3.0 Hz, NCH), 8.46 (1H, d, *J*=4.0 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 18.09 (Ar–*Me*$_2$), 28.04 and 28.56 (2OC*Me*$_3$), 80.94 and 82.36 (2O*C*Me$_3$), 89.69 (C$_{spiro}$), 118.47, 122.15, 122.37, 124.63, 125.93, 126.78, 128.23, 133.88, 135.23, 137.22, 138.53, 138.91, 146.10, 150.14, 154.68 and 159.71 (C=C$_{iminolactone}$ and C$_{arom}$), 162.98 (C=N), 163.97, 167.29 and 191.15 (3C=O). MS (*m/z*, %): 569 (M$^+$+2, 9), 568 (M$^+$+1, 7), 567 (M$^+$, 7), 463 (2), 453 (7), 349 (2), 121(100), 120 (52), 57 (70), 41 (24). Anal Calcd for $C_{33}H_{33}N_3O_6$ (567.63): C, 69.83; H, 5.86; N, 7.40%; Found: C, 69.78; H, 5.80; N, 7.42%.

5: Pale powder. m.p. 164.5–167.5 °C, yield: 0.60 g (92%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1756 and 1730 (4C=O), 1696 (2C=N). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.33 (18H, s, 2C*Me*$_3$), 3.25 (6H, s, 2O*Me*), 3.82 (6H, s, 2O*Me*), 7.39 (2H, dd, J_1=7.5, J_2=4.54 Hz, 2CH), 7.57 (2H, d, *J*=7.5 Hz, 2CH), 8.86 (2H, d, *J*=4.5 Hz, 2NCH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 29.49 (2C*Me*$_3$), 52.79 and 53.16 (4O*Me*), 55.71 (2N-*C*Me$_3$), 91.23 (2C$_{spiro}$), 124.89, 125.77, 130.87, 133.16, 134.99, 149.58, 150.19 (C=C$_{iminolactone}$ and C$_{arom}$), 152.75 (2C=N$_{imin}$), 158.98 and 160.99 (4CO of esters); MS (*m/z*, %): 662



Scheme 3

(M^++2, 21), 661 (M^++1, 24), 646 (4), 604 (36), 573 (7), 57 (100), 41 (69). Anal Calcd for $C_{34}H_{36}N_4O_{10}$ (660.67): C, 61.81; H, 5.49; N, 8.48%; Found: C, 61.42; H, 5.25; N, 8.52%.

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