γ-Dispiro-iminolactone synthesis by three component reaction between alkyl isocyanides and acetylenic esters with α- dicarbonyl compounds

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Abstract
The three-component coupling reaction between α-dicarbonyl compounds and dialkyl acetylene-dicarboxylates with isocyanides proceeds efficiently to afford the corresponding γ-dispiro-iminolactones in high yields.

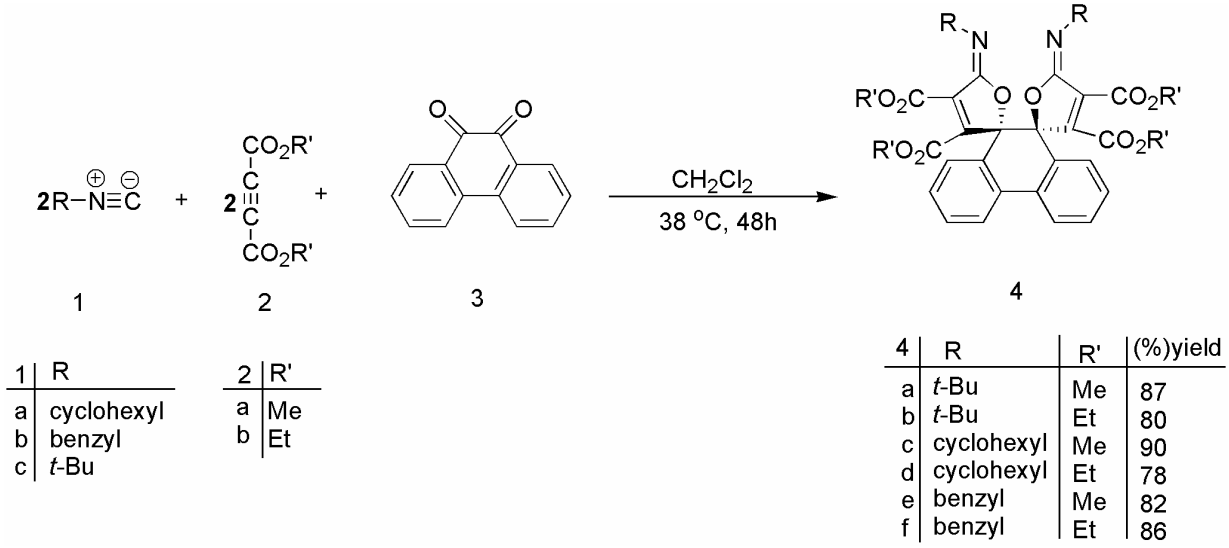
Keywords: Acetylenic esters, γ-dispiro-iminolactones, isocyanides, three-component reaction, phenanthraquinone, aceanthraquinone

Introduction

The art of performing multi-component coupling reactions in a one-pot operation has received considerable interest due to generate molecular diversity and complexity.[1] Recently γ-spiro-iminolactones have been the subject of great consideration because of their effects as antibacterial agents, aldosterone inhibitors and proper precursors for the preparation of a wide spectrum of natural compounds.[2] Iminolactones could be hydrolyzed with aqueous hydrochloric acid to produce butenolides,[3] (also named furan-2(5*H*)-ones)[4] they are an important class of natural products that are biologically active compounds which is used in medicine and agriculture.[5-9] In our current studies on the investigation of the reaction between isocyanides and α-dicarbonyl compounds in the presence of acetylenic esters, we wish to report a simple one-pot synthesis of γ-dispiro-iminolactones.[10-14]

Results and Discussion

The reaction between alkyl isocyanides and phenanthraquinone or aceanthraquinone in the presence of dialkyl acetylenedicarboxylates could afford products that were characterized as **4a-f** and **6** (see Scheme 1 and 2 respectively).[10-14]

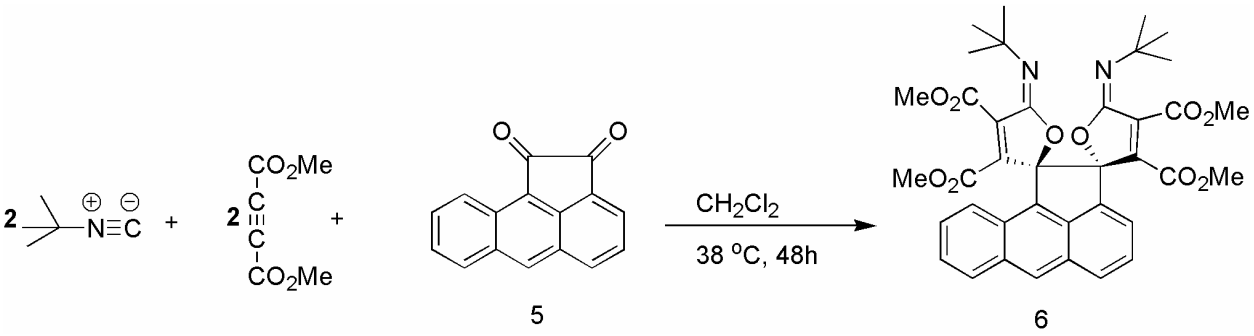


1	R
a	cyclohexyl
b	benzyl
c	*t*-Bu

2	R'
a	Me
b	Et

4	R	R'	(%)yield
a	*t*-Bu	Me	87
b	*t*-Bu	Et	80
c	cyclohexyl	Me	90
d	cyclohexyl	Et	78
e	benzyl	Me	82
f	benzyl	Et	86

Scheme 1

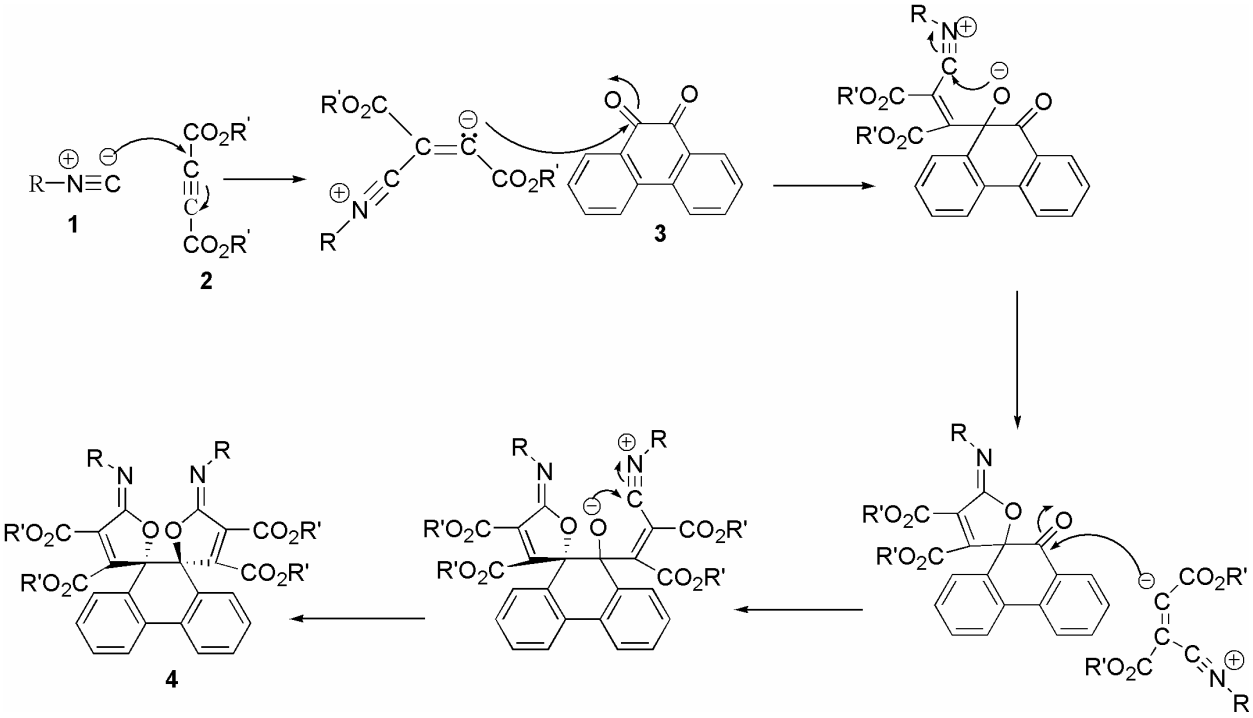


Scheme 2

Products **4a-f** and **6** are stable solids whose structures were deduced from IR, ^{1}H- and ^{13}C NMR and mass spectra. The IR spectrum of compounds **4a** showed strong absorption at 1740 and 1693 cm^{-1} due to the ester groups and also 1647 cm^{-1} due to C=N. The ^{1}H- NMR spectrum of **4a** exhibited one singlet arising from the *tert*-butyl groups (δ=1.40 ppm) and two singlets from the methoxycarbonyl groups (δ=3.14 and 3.76 ppm) (see Experimental section). The ^{13}C- NMR spectrum of **4a** showed 16 distinct resonances, which are consistent with the γ-dispiro-iminolactone structure. The characteristic signal of the spiro carbon was recognized at δ92.04

(Experimental section). The Mass spectrum of this compound **4a** displayed a molecular-ion peak at the appropriate *m/z* value. The spectroscopic behaviors of **4b-f** are similar to those of **4a,** except for the isocyanide and ester residues. The ^{1}H- NMR spectra of compounds **4e** and **4f** show an AB quartet for the benzylic CH_2, consistent with the chiral structure (a racemic product). The formation of the products **4a-f** could be rationalized as shown in Scheme 3.

In further investigations, similar reactivity was observed for the reaction between aceanthraquinone **5** and dimethyl acetylenedicarboxylate (DMAD) in the presence of *tert*-butyl isocyanide to yield the γ-dispiro-iminolactone **6** in good yield (Scheme 2).



Scheme 3

Experimental Section

General Procedures. Dialkyl acetylenedicarboxylates,; *tert*-butyl-, cyclohexyl- and benzyl-isocyanides, phenanthrenequinone, and aceanthrenequinone were purchased from Merck and Fluka, respectively, and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and Shimadzu IR-470 spectrometer respectively. The ^{1}H- and ^{13}C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 and 75.5 MHz, respectively. Elemental analyses for C, H and N using a Heraeus CHN-O-Rapid analyzer were carried out at the research laboratory of Tarbiat Moallem University of Tehran. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX

mass spectrometer operating at an ionization potential of 70 eV at research laboratory center of Shahid Beheshty University of Tehran.

General preparative procedure (exemplified by 4a). The solution of *tert*-butyl isocyanide (0.10 g, 1.2 mmol) in 3 mL of CH_2Cl_2 solvent was slowly added dropwise to the mixture of phenanthrenequinone (0.104 g, 0.5 mmol) and DMAD (0.171 g, 1.2 mmol) in 20 mL of dry CH_2Cl_2 for 5 min at RT. After the addition, the solution was heated to 38 °C for 48h. Then, the whole reaction mixture had solidified into a solid product, the solvent was removed by filtration, and the crystals of product were washed with cold diethyl ether (2×5 mL).

Bis-(dimethyl-2-*tert*-butylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4a). Light brown crystals, 0.27 g, yield 87%, mp 145-148 °C. IR (KBr) (ν_{max}, cm^{-1}): 1693 and 1740 (4 C=O), 1647 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 1.40 (18H, s, 2 C*Me*$_3$), 3.14, 3.76 (12H, 2s, 4 O*Me*), 7.33 (2H, br. s, 2 CH), 7.36 (2H, br. s, 2 CH), 7.47 (2H, br. s, 2 CH), 7.80 (2H, br. s, 2 CH). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 29.49 (2 C*Me*$_3$), 52.22 and 52.67(4 O*Me*), 55.05 (2 N*C*Me$_3$), 92.04 (2 C_{spiro}), 123.60, 125.26, 128.94, 130.24 (2C_{arom}), 130.83, 133.53 and 150.38 (C=$C_{iminolactone\ ring}$ and C_{arom}), 150.84 (2 N=$C_{iminolactone}$), 160.69 and 161.82 (4C=O of esters). MS, (*m/z*, %): 659 (M^++1, 3), 658 (M^+, 14), 602 (100), 546 (18), 514 (4), 497 (3), 437 (3), 406 (3), 350 (5), 314 (3), 258 (2), 196 (10), 57 (34). Anal. Calcd for $C_{36}H_{38}N_2O_{10}$ (658): C, 65.65; H, 5.77; N, 4.25. Found: C, 66.71; H, 5.85; N, 4.32.

Bis-(diethyl-2-*tert*-butylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4b). Pale yellow powder, 0.28 g, yield 80%, mp 146-149 °C, IR (KBr) (ν_{max}, cm^{-1}): 1723 and 1739 (4 C=O), 1684 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 0.89 (6H, t, *J*=7.0 Hz, 2 OCH$_2$*CH*$_3$), 1.23 (6H, t, *J*=7.0 Hz, 2 OCH$_2$*CH*$_3$), 1.41 (18H, s, 2 C*Me*$_3$), 3.58 (4H, m, 2 O*CH*$_2$CH$_3$), 4.24 (4H, m, 2 O*CH*$_2$CH$_3$), 7.28–7.42 (6H, m, 6 CH), 7.82 (2H, d, *J*= 6.5 Hz, 2 CH). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 13.39 and 13.84 (4 OCH$_2$*C*H$_3$), 29.53 (2 C*Me*$_3$), 55.25 (2 N*C*Me$_3$), 60.95 and 61.81 (4 OCH$_2$CH$_3$), 92.23 (2 C_{spiro}), 123.52, 125.60, 128.98, 129.78, 130.33, 130.63, 133.42 and 150.21 (C=$C_{iminolactone\ ring}$ and C_{arom}), 150.98 (2 N=$C_{iminolactone}$), 160.09 and 161.28 (4C=O of esters). MS, (*m/z*, %): 714 (M^+, 8), 659 (100), 602 (27), 557 (6), 378 (10), 288 (4), 168 (10), 57 (13). Anal. Calcd for $C_{40}H_{46}N_2O_{10}$ (714): C, 67.23; H, 6.44; N, 3.92. Found: C, 67.53; H, 6.39; N, 4.18.

Bis-(dimethyl-5-cyclohexylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4c). White powder, 0.31 g, yield 90%, mp 166-169 °C, IR (KBr) (ν_{max}, cm^{-1}): 1684 and 1742 (4 C=O), 1645 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 1.25-1.77 (20H, m, 10 CH_2), 3.17 (6H, s, 2 OMe), 3.61 (2H, m, 2 N-C*H*), 3.80 (6H, s, 2 OMe), 7.28 (2H, d, *J*=6.7 Hz, 2 CH), 7.36 (2H, t, *J*=5.8 Hz, 2 CH), 7.46 (2H, t, *J*=6.4 Hz, 2 CH) and 7.81 (2H, d, *J*=6.9 Hz, 2 CH). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 24.88, 24.94, 25.63, 32.87 and 33.15 (10 CH_2), 52.37 and 52.95 (4 OMe), 57.50 (2 N-*C*H), 92.33 (2 C_{spiro}), 123.54, 125.28 (2 C_{arom}), 128.95, 130.35, 130.13, 133.65 and 150.29 (C=$C_{iminolactone\ ring}$ and C_{arom}), 155.73 (2 C=$N_{iminolactone}$), 160.68 and 161.32 (4 C=O of esters). MS, (*m/z*, %): 710 (M^+, 6), 628 (53), 432 (8), 196 (24), 180 (8), 111

(17), 83 (35), 59 (33), 55 (100). Anal. Calcd for $C_{40}H_{42}N_2O_{10}$ (710): C, 67.61; H, 5.92; N, 3.94. Found: C, 67.98; H, 5.83; N, 4.03.

Bis-(diethyl-5-cyclohexylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4d). White powder, 0.29 g, yield 78%, mp 179-182 °C, IR (KBr) (ν_{max}, cm^{-1}): 1736 and 1685 (4 C=O), 1641 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 0.90 (6H, t, *J*=7.0 Hz, 2 OCH_2CH_3), 1.20-1.90 (20H, m, 10 CH_2), 1.25 (6H, t, *J*=7.0 Hz, 2 OCH_2CH_3), 3.53 (2H, m, 2 N-C*H*), 3.68 (4H, m, 2 OCH_2CH_3), 4.28 (4H, m, 2 OCH_2CH_3), 7.30 (2H, d, *J*=7.9 Hz, 2 CH), 7.38 (2H, t, *J*=7.5 Hz, 2 CH), 7.48 (2H, t, *J*=7.2 Hz, 2 CH), 7.83 (2H, d, *J*=7.6 Hz, 2 CH). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 13.40 and 13.91 (4 OCH_2CH_3), 24.95, 25.76, 32.91 and 33.16 (10 CH_2), 57.42 (2 N-*C*H), 61.61 and 61.74 (4 OCH_2CH_3), 91.32 (2 C_{spiro}), 123.40, 125.43, 128.84, 129.33, 130.17, 130.72, 133.46 and 150.20 (C=$C_{iminolactone\ ring}$ and C_{arom}), 153.48 (2 C=$N_{iminolactone}$), 160.06 and 161.18 (4 C=O of esters). MS, (*m/z*, %): 767 (M^++1, 6), 766 (M^+, 13), 720 (13), 693 (13), 684 (37), 594 (10), 460 (26), 259 (13), 168 (38), 83 (29), 55 (100). Anal. Calcd for $C_{44}H_{50}N_2O_{10}$ (766): C, 68.93; H, 6.53; N, 3.66. Found: C, 69.57; H, 6.59; N, 3.56.

Bis-(dimethyl-5-benzylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4e). Pale yellow powder, 0.30 g, yield 82%, mp 93-96 °C, IR (KBr) (ν_{max}, cm^{-1}): 1739 and 1686 (4C=O), 1648 (2C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 3.19 (6H, br s, 2 OMe), 3.83 (6H, br s, 2 OMe), 4.75 (4H, AB quartet, 2 CH_2 of benzyl), 7.00-7.79 (18H, m, 16 CH_{arom}). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 52.48 and 52.80 (4 OMe), 53.00 (2 N-*C*H_2), 91.63 (2 C_{spiro}), 123.63, 125.43, 126.69, 128.10, 128.27, 128.36, 128.88, 130.44, 131.10, 133.59, 139.46 and 151.32 (C=$C_{iminolactone\ ring}$ and C_{arom}), 155.46 (2 C=N_{imine}), 160.59 and 161.48 (4 C=O of esters). MS, (*m/z*, %): 726 (M^+, 5), 667 (14), 635(6), 608 (4), 593 (21), 490 (3), 208 (3), 91 (100). Anal. Calcd for $C_{42}H_{34}N_2O_{10}$ (726): C, 69.42; H, 4.68; N, 3.86. Found: C, 70.65; H, 4.76; N, 3.92.

Bis-(diethyl-5-benzylimino-5*H*,6*H*')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetra-carboxylate (4f). Pale yellow powder, 0.34 g, yield 86%, mp 141-144 °C, IR (KBr) (ν_{max}, cm^{-1}): 1734 and 1684 (4 C=O), 1645 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 0.92 (6H, t, *J*=6.8, 2 OCH_2CH_3), 1.27 (6H, t, *J*=6.7 Hz, 2 OCH_2CH_3), 3.64 (4H, m, 2 OCH_2CH_3), 4.35(4H, m, 2 OCH_2CH_3), 4.80 (4H, AB quartet, 2 CH_2 of benzyl), 6.93 (2H, d, J=5.9 Hz, 2 CH), 7.26 (14H, m, 14 CH), 7.80 (2H, d, *J*=7.6 Hz, 2 CH). ^{13}C NMR (75.4 MHz, δ, $CDCl_3$): 13.43 and 13.91 (4 OCH_2CH_3), 52.26 (2 N-*C*H_2), 61.92 and 62.15 (4 OCH_2CH_3), 92.03 (2 C_{spiro}), 123.45, 125.56, 126.71, 128.26, 128.34, 128.86, 129.27, 129.71, 130.41, 133.55, 139.44 and 150.79 (C=$C_{iminolactone\ ring}$ and C_{arom}), 150.79 (2 C=$N_{iminolactone}$), 160.05 and 160.88 (4 C=O of esters). MS, (*m/z*, %): 782 (M^+, 4), 710 (4), 646 (3), 471 (2), 197 (2), 168 (5), 132 (6), 91 (100). Anal. Calcd for $C_{46}H_{42}N_2O_{10}$ (782): C, 70.59; H, 5.38; N, 3.59. Found: C, 71.60; H, 5.41; N, 3.65.

Bis-(dimethyl-5-*tert*-butylimino-1*H*-2*H*')-dispiro[furan-2,5'-aceanthrylene]-3,3',4,4'-tetra-carboxylate (6). Light yellow powder, 0.31 g, yield 91%, mp 240-242 °C, IR (KBr) (ν_{max}, cm^{-1}): 1734 and 1745 (4 C=O), 1681 (2 C=N). ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 1.29 (9H, s, C*Me*$_3$), 1.30 (9H, s, C*Me*$_3$), 3.26 (3H, s, OMe), 3.28 (3H, s, OMe), 3.94 (6H, s, 2 OMe), 7.28 (1H, dd, J_1=1.8, J_2=5.0 Hz, CH), 7.48-7.60 (3H, m, 3 CH), 7.70 (1H, d, *J*=7.8 Hz, CH), 8.0 (1H, d, *J*=8.6 Hz, CH_{arom}), 8.14 (1H, dd, J_1=1.8, J_2=7.3 Hz, CH) and 8.50 (1H, s, CH). ^{13}C NMR (75.4

MHz, δ, $CDCl_3$): 29.41 and 29.47 (2 C*Me*$_3$), 52.06, 52.10, 52.99 and 53.04 (4 OMe), 55.31 and 55.46 (2 N*C*Me$_3$), 101.43 and 102.67 (2 C_{spiro}), 118.53, 119.04, 122.46, 125.48, 125.72, 126.32, 126.68, 126.89, 127.19, 127.43, 128.05, 130.27, 130.66, 134.12, 136.40, 137.29, 138.04 and 141.33 (C=$C_{iminolactone\ ring}$ and C_{arom}), 151.91 and 152.13 (2 C=N_{imine}), 160.01, 160.07, 162.11 and 162.24 (4 C=O of esters). MS, (*m/z*, %): 682 (M^+, 3), 626 (6), 494 (4), 467 (8), 342 (8), 314 (6), 282 (6), 254 (5), 196 (4), 84 (5), 57 (100). Anal. Calcd for $C_{38}H_{38}N_2O_{10}$ (682): C, 66.86; H, 5.57; N, 4.11. Found: C, 67.25; H, 5.61; N, 3.93.

Acknowledgements

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