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

Nourollah Hazeri,a Malek Taher Maghsoodlou,a,* Sayyed Mostafa Habibi-Khorassani,a Morteza Ziyaadini,a Ghasem Marandi,a Khatereh Khandan-Barani,a and Hamid Reza Bijanzadeh b

aDepartment of Chemistry, the University of Sistan and Balouchestan, P. O. Box 98135-674, Zahedan, Iran
bDepartment of Chemistry, Tarbiat Moallem University, Tehran, Iran
E-mail: mt_maghsoodlou@yahoo.com

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, phenantraquinone, 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(5H)-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

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 ($\delta=1.40$ ppm) and two singlets from the methoxycarbonyl groups ($\delta=3.14$ and 3.76 ppm) (see Experimental section). The $^{13}$C- NMR spectrum of 4a showed 16 distinct resonances, which are consistent with the $\gamma$-dispiro-iminolactone structure. The characteristic signal of the spiro carbon was recognized at $\delta$92.04
(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 1H- NMR spectra of compounds 4e and 4f show an AB quartet for the benzylic CH₂, 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](image_url)

**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 1H- and 13C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with CDCl₃ 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$_2$Cl$_2$ 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$_2$Cl$_2$ for 5 min at RT. After the addition, the solution was heated to 38 ºC 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-5H,6H')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetracarboxylate (4a).** Light brown crystals, 0.27 g, yield 87%, mp 145-148 ºC. IR (KBr) ($\nu_{\text{max}}$, cm$^{-1}$): 1693 and 1740 (4 C=O), 1647 (2 C=N). 1H NMR (300.1 MHz, $\delta$, CDCl$_3$): 1.40 (18H, s, 2 CMe$_3$), 3.14, 3.76 (12H, 2s, 4 OMe), 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). 13C NMR (75.4 MHz, $\delta$, CDCl$_3$): 29.49 (2 CMe$_3$), 52.22 and 52.67 (4 OMe), 55.05 (2 N-CMe$_3$), 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$_2$O$_{10}$ (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-5H,6H')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetracarboxylate (4b).** Pale yellow powder, 0.28 g, yield 80%, mp 146-149 ºC, IR (KBr) ($\nu_{\text{max}}$, cm$^{-1}$): 1723 and 1739 (4 C=O), 1684 (2 C=N). 1H NMR (300.1 MHz, $\delta$, 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 CMe$_3$), 3.58 (4H, m, 2 OCH$_2$CH$_3$), 4.24 (4H, m, 2 OCH$_2$CH$_3$), 7.28–7.42 (6H, m, 6 CH), 7.82 (2H, d, $J$= 6.5 Hz, 2 CH). 13C NMR (75.4 MHz, $\delta$, CDCl$_3$): 13.39 and 13.84 (4 OCH$_2$C), 29.53 (2 CMe$_3$), 55.25 (2 NMe$_3$), 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 (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$_{40}$H$_{46}$N$_2$O$_{10}$ (714): C, 67.23; H, 6.44; N, 3.92. Found: C, 67.53; H, 6.39; N, 4.18.

**Bis-(dimethyl-5-cyclohexylimino-5H,6H')-dispiro[furan-2,5'-phenanthrene]-3,3',4,4'-tetracarboxylate (4c).** White powder, 0.31 g, yield 90%, mp 166-169 ºC, IR (KBr) ($\nu_{\text{max}}$, cm$^{-1}$): 1684 and 1742 (4 C=O), 1645 (2 C=N). 1H NMR (300.1 MHz, $\delta$, CDCl$_3$): 1.25-1.77 (20H, m, 10 CH$_2$), 3.17 (6H, s, 2 OMe), 3.61 (2H, m, 2 N-CH), 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). 13C NMR (75.4 MHz, $\delta$, CDCl$_3$): 24.88, 24.94, 25.63, 32.87 and 33.15 (10 CH$_2$), 57.50 (2 N-CH), 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
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), 1.20-1.90 (2OCH₂CH₃), 1.25 (6H, t, J=7.0 Hz, 2 OCH₂CH₃), 3.53 (2H, m, 2 N-CH₃), 3.64 (4H, m, 2 OCH₂CH₃), 7.30 (2H, d, J=7.9 Hz, 2 CH), 7.38 (2H, J=7.5 Hz, 2 CH), 7.48 (2H, J=7.2 Hz, 2 CH), 7.83 (2H, d, J=7.6 Hz, 2 CH). ¹H NMR (300.1 MHz, δ, CDCl₃): 0.90 (6H, t, J=7.0 Hz, 2 OCH₂C₂H₅), 1.20-1.90 (20H, m, 10 CH₂), 1.25 (6H, t, J=7.0 Hz, 2 OCH₂C₂H₅), 3.53 (2H, m, 2 N-C₇H₅), 3.68 (4H, m, 2 OCH₂C₂H₅), 4.28 (4H, m, 2 OCH₂C₂H₅), 7.30 (2H, d, J=7.9 Hz, 2 CH), 7.38 (2H, t, J=7.5 Hz, 2 CH), 7.48 (2H, J=7.2 Hz, 2 CH), 7.83 (2H, d, J=7.6 Hz, 2 CH). ¹³C NMR (75.4 MHz, δ, CDCl₃): 13.40 and 13.91 (4 OCH₂C₂H₅), 24.95, 25.76, 32.91 and 33.16 (10 CH₂), 57.42 (2 N-C₇H₅), 61.61 and 61.74 (4 OCH₂C₂H₅), 91.32 (2 C₇H₅), 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), 425 (26), 259 (13), 168 (38), 83 (29), 55 (100). Anal. Calcd for C₄₄H₅₀N₂O₁₀ (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), 4.75 (4H, AB quartet, 2 CH₂ of benzyl), 2.99-7.76 (18H, m, 16 CH arom). ¹H NMR (300.1 MHz, δ, CDCl₃): 3.19 (6H, br s, 2 OMe), 3.83 (6H, br s, 2 OMe), 4.75 (4H, AB quartet, 2 CH₂ of benzyl), 7.00-7.79 (18H, m, 16 CH arom). ¹³C NMR (75.4 MHz, δ, CDCl₃): 52.48 and 52.80 (4 OMe), 53.00 (2 N-C₇H₅), 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 C₄₂H₃₄N₂O₁₀ (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 1685 (4C=O), 1.27 (6H, t, J=6.8 Hz, 2 OCH₂CH₃), 1.25 (6H, t, J=6.7 Hz, 2 OCH₂CH₃), 3.64 (4H, m, 2 OCH₂CH₃), 7.28 (1H, dd, J=1.8, J=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, J₁=1.8, J₂=7.3 Hz, CH) and 8.50 (1H, s, CH). ¹³C NMR (75.4 MHz, δ, CDCl₃): 13.43 and 13.91 (4 OCH₂C₂H₅), 52.26 (2 N-CH₃), 61.92 and 62.15 (4 OCH₂CH₃), 92.03 (2 C₇H₅), 123.45, 125.56, 126.71, 128.26, 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 C₄₆H₄₂N₂O₁₀ (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 86%, mp 240-242 °C, IR (KBr) (ν_max, cm⁻¹): 1734 and 1745 (4 C=O), 1681 (2 C=N). ¹H NMR (300.1 MHz, δ, CDCl₃): 0.92 (6H, t, J=6.8, 2 OCH₂CH₃), 1.27 (6H, t, J=6.7 Hz, 2 OCH₂CH₃), 3.64 (4H, m, 2 OCH₂CH₃), 4.35(4H, m, 2 OCH₂CH₃), 4.80 (4H, AB quartet, 2 CH₂ 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). ¹³C NMR (75.4 MHz, δ, CDCl₃): 13.43 and 13.91 (4 OCH₂CH₃), 52.26 (2 N-CH₃), 61.92 and 62.15 (4 OCH₂CH₃), 92.03 (2 C₇H₅), 123.45, 125.56, 126.71, 128.26, 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 C₄₆H₄₂N₂O₁₀ (782): C, 70.59; H, 5.38; N, 3.59. Found: C, 71.60; H, 5.41; N, 3.65.
MHz, δ, CDCl₃): 29.41 and 29.47 (2 CMe₃), 52.06, 52.10, 52.99 and 53.04 (4 OMe), 55.31 and 55.46 (2 NCOME), 101.43 and 102.67 (2 Cspiro), 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=Ciminolactone ring and Carom), 151.91 and 152.13 (2 C=Nimine), 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 C₃₈H₃₈N₂O₁₀ (682): C, 66.86; H, 5.57; N, 4.11. Found: C, 67.25; H, 5.61; N, 3.93.

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