Synthesis of Stable Atropisomers of Dialkyl-4-Ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates

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Summary. Protonation of the reactive 1:1-intermediate produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates with diethyl *N,N′*-(naphthalene-1,8-diyl)-dioxamate leads to a vinylphosphonium salt which undergoes an intramolecular *Wittig* reaction to produce dialkyl-4-ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates in good yields. The title compounds exist as stable rotamers as a result of restricted rotation around the single bond linking the naphthalene moiety and the heterocyclic system. The calculated free energy of activation for interconversion of the atropisomers amounts to about $102 \pm 2 \, kJ \cdot mol^{-1}$.

Keywords. *Peri* interaction; Hindered rotation; Stereochemistry; Rotational isomers; Intramolecular *Wittig* reaction; Triphenylphosphine.

Introduction

House and coworkers [1] have shown that 1,8-diarylnaphthalenes, including 1,8-bis-(3-chlorophenyl)-naphthalene and 1,8-bis-(3-methylcarboxyphenyl)-naphthalene, cannot be resolved into stable configurational isomers due to a dynamic equilibrium at room temperature between *cis*- and *trans*-atropisomers with rotational energy barriers in the range of $40–65 \, kJ \cdot mol^{-1}$. The isolation of stable *cis*- and *trans*-isomers of this type is a challenging task. Related atropisomers have been separated [2] for 1,8-di-*o*-tolylnaphthalene as a result of its high rotational energy barrier ($100.9 \, kJ \cdot mol^{-1}$). We now have found that dialkyl-4-ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates (**3**) exhibit atropisomerism at ambient temperature, and that these isomers can be separated by fractional crystallization. Compound **3** is readily prepared *via* an intramolecular *Wittig* reaction [3–7]. Triphenylphosphine and dialkyl acetylenedicarboxylates undergo a smooth reaction in the presence of a strong NH-acid such as diethyl *N,N′*-(naphthalene-1,8-diyl)-dioxamate (**2**; [8]) at ambient temperature to produce a phosphorus ylide. This in turn experiences an

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intramolecular *Wittig* reaction under the reaction conditions employed to afford highly functionalized 5-oxo-4,5-dihydropyrrole derivatives (**3**) in excellent yields. Compounds **3** exhibit atropisomerism [9] at ambient temperature because of hindered rotation about the carbon–nitrogen bond between the naphthalene moiety and the pyrrole ring system as a result of the *peri*-interaction [10] of the pyrrole moiety with the adjacent *N*-oxamate chain.

Results and Discussion

The reaction of dialkyl acetylenedicarboxylates with diethyl *N,N'*-(naphthalene-1,8-diyl)-dioxamate in the presence of triphenylphosphine proceeded spontaneously at ambient temperature in dichloromethane and was complete within a few hours. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of a nearly 1:1-mixture of two isomeric forms of dialkyl 4-ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **3** (Scheme 1).

The structures of compounds **3a** and **3b** were deduced from their elemental analyses and their NMR and IR spectroscopic data. The mass spectra of **3a**, **b** were fairly similar and displayed molecular ion peaks at $m/z = 484$ and 568, respectively. Initial fragmentations involved the loss of the ester moieties and scission of the heterocyclic ring system.

Although the mechanism of the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of diethyl *N,N'*-(naphthalene-1,8-diyl)-dioxamate has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [3–5] it is reasonable to assume that **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1-adduct by the NH-acid. Then, the positively charged ion might be attacked by the conjugate base of the NH-acid to form
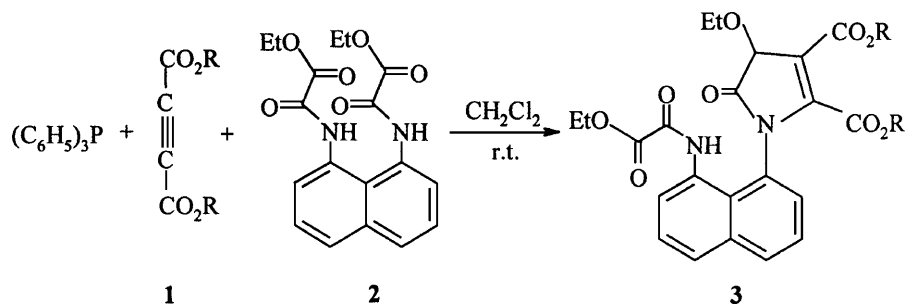
| 1, 3	R	Yield/%
a	^{t}Bu	90
b	Me	95

Scheme 1
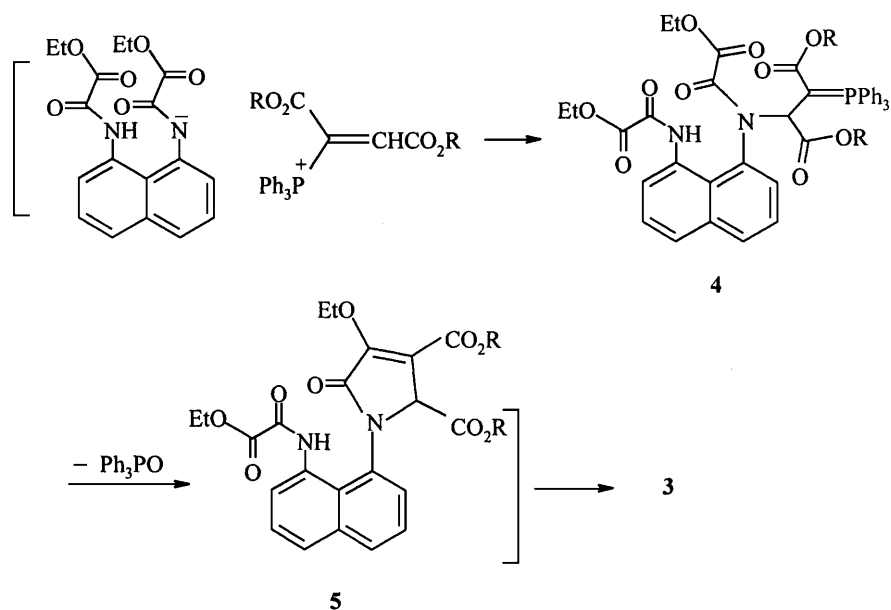
Scheme 2

phosphorane **4** which in turn is converted to pyrrole derivative **5**. Isomerization under the reaction conditions employed affords the 5-oxo-4,5-dihydropyrrole ring system **3** in excellent yield (Scheme 2).

^{13}C NMR spectroscopy was used to distinguish **3** from the primary adduct **5**. The ^{13}C NMR spectrum of each isolated product exhibited a methine carbon resonance at about 68–69 ppm. The chemical shift of the methine carbon in **5** is expected to amount to about 52–56 ppm [11, 12].

The ^{1}H and ^{13}C NMR spectra of compounds **3a** and **3b** clearly indicated the presence of two rotational isomers **I** and **II** (Scheme 3). In case of **3a**, these rotamers can be separated by fractional crystallization from hexane/ethyl acetate. Thus, pale orange crystals of **3a-I** (60%, m.p.: 112–115°C) and colorless needles of **3a-II** (40%, m.p.: 91–93°C) were obtained. The ^{1}H NMR spectrum of **3a-I** exhibit three sharp singlets, readily recognizable as arising from the *tert*-butoxy (1.07 and 1.56 ppm) and methine (5.21 ppm) protons, along with characteristic
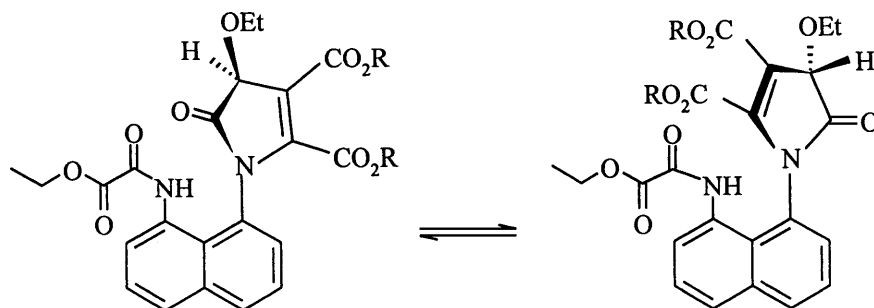
Scheme 3

Table 1. Equilibrium constants, standard *Gibbs* energies, and selected activation parameters for the conversion of **3b-I** to **3b-II** in CDCl$_3$

T_c/K	$\Delta G°$/kJ $\cdot$ mol^{-1}	k/s^{-1}	$\Delta H^{\neq}$/kJ $\cdot$ mol^{-1}	$\Delta S^{\neq}$/J $\cdot$ mol^{-1} $\cdot$ K^{-1}	$\Delta G^{\neq}$/kJ $\cdot$ mol^{-1}
298	1.61	1.84×10^{-4}	101.90	-1.59	102.38
310	0.96	3.60×10^{-5}	101.80	-1.92	102.40
323	0.84	7.04×10^{-6}	101.70	-2.26	102.43

multiplets for the two ethoxy groups. The protons of the naphthalene residue appear as a complex multiplet in the aromatic region, whereas the NH group gives rise to a fairly sharp band at 10.43 ppm. The ^{13}C NMR spectrum of **3a-I** exhibits twenty-six resonances in agreement with the structure of **3**. Partial assignments of these resonances are given in the Experimental section. Although the ^{1}H and ^{13}C NMR spectra of compound **3a-II** are similar to those of **3a-I**, significant differences in the chemical shifts can be noticed (see Experimental).

The NMR spectra of **3b** indicated the presence of two rotamers **3b-I** and **3b-II** in a 2:1 ratio. The major isomer crystallized as colorless crystals (m.p.: 178–180°C, hexane/ethyl acetate). The ^{1}H NMR spectrum of the mother liquor showed the resonances of both isomers in the original ratio. We were not able to isolate **3b-II** in pure form; however, its NMR data can be extracted from the mixture of the two atropisomers (see Experimental).

First-order kinetics were observed for the interconversion of **3b-I** and **3b-II** in CDCl$_3$ at 298, 310, and 323 K by proton NMR, starting with either a single isomer or a nonequilibrium mixture. The ratio of the two atropisomers was measured by integration of the well-resolved ^{1}H resonances of the methoxy groups and varied between 0.52 at 298 K to 0.73 at 323 K, corresponding to free-energy differences of 1.61 and 0.84 kJ $\cdot$ mol^{-1} (Table 1).

The time-dependent interconversion of **3b-I** and **3b-II** was measured at 298, 310, and 323 K, and the rate coefficient was determined by integration of the methoxy resonances. The rate coefficient varied in from 1.84×10^{-4} s^{-1} at 298 K to 7.04×10^{-6} s^{-1} at 323 K, and plots of ln$k$ *vs.* T^{-1} (*Arrhenius*) and ln(k/T) *vs.* T^{-1} (*Eyring*) were both linear. The former plot yielded 104.38 kJ $\cdot$ mol^{-1} for the *Arrhenius* activation energy and 1.39×10^{13} for the *Arrhenius* A-factor at 298 K. The activation parameters are given in Table 1; $\Delta G^{\neq}$ of the reaction **3b-I**⇌**3b-II** is slightly higher than the value reported for 1,8-di-*o*-tolylnaphthalene [2].

Experimental

Dialkyl acetylenedicarboxylates, triphenylphosphine, ethyl oxalylchloride, and naphthalene-1,8-diamine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses (C, H, N) were performed using a Heraeus CHN–O-Rapid analyzer; the results agreed favourably with the calculated values. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured in CDCl$_3$ with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared using Aldrich silica gel 70–230 mesh.

Preparation of **3**; *general procedure*

To a stirred solution of 0.52 g triphenylphosphine (2 mmol) and 0.70 g diethyl-*N,N'*-(naphthalene-1,8-diyl)-dioxamate (**2**; 2 mmol) in 6 cm^3 CH$_2$Cl$_2$, a mixture of 0.45 g di-*tert*-butyl acetylenedicarboxylate (2 mmol) in 4 cm^3 CH$_2$Cl$_2$ was added at $-5°$C over 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane:ethyl acetate = 2:1). The solvent was removed under reduced pressure, and the product was recrystallized from hexane:ethyl acetate = 1:1.

Di-tert-butyl-4-ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**3a**; C$_{30}$H$_{36}$N$_2$O$_9$)

3a-I: pale orange crystals; m.p.: 112–115°C; yield: 0.62 g (65%); IR (KBr): $\nu = 3260$ (N–H), 1741, 1708 (C=O) cm^{-1}; MS: m/z (%) = 569 (M$^+$, 5), 514 (12), 438 (50), 394 (48), 291 (28), 168 (15), 57 (100); ^{1}H NMR: $\delta = 1.07$ (9H, s, C(CH$_3$)$_3$), 1.41 and 1.44 (6H, 2t, $J = 7.1$ Hz, 2 CH$_2$CH$_3$), 1.56 (9H, s, C(CH$_3$)$_3$), 4.43 (2H, q, $J = 7.1$ Hz, CH$_2$CH$_3$), 4.70 and 4.87 (2H, 2dq, $^2J_{HH} = 10.1$ Hz, $^3J_{HH} = 7.1$ Hz, AMX$_3$ system, CHOCH$_2$CH$_3$), 5.21 (1H, s, CH), 7.34 (1H, d, $J = 7.3$ Hz, CH), 7.52 (1H, t, $J = 7.7$ Hz, CH), 7.56 (1H, t, $J = 7.9$ Hz, CH), 7.81 (1H, d, $J = 8.2$ Hz, CH), 7.93 (1H, d, $J = 8.2$ Hz, CH), 8.06 (1H, d, $J = 7.5$ Hz, CH), 10.43 (1H, s, NH) ppm; ^{13}C NMR: $\delta = 13.98$ and 15.71 (2 CH$_3$), 27.44 and 28.12 (2 C(CH$_3$)$_3$), 63.12 and 65.79 (2 OCH$_2$), 68.29 (OCH), 82.05 and 83.81 (2 CMe$_3$), 114.89 (N–C=C), 125.06 (C), 125.20, 125.33, 126.35, 127.38, 127.51 (5 CH), 130.45 (C), 130.62 (CH), 130.14, 136.02, 153.18 (3 C), 154.99, 160.76, 160.96, 166.10, 167.44 (5 C=O) ppm.

    3a-II: colorless crystals; m.p.: 91–93°C; yield: 0.40 g (35%); IR (KBr): $\nu = 3330$ (N–H), 1710 (C=O) cm^{-1}; MS: m/z (%) = 569 (M$^+$, 10), 514 (15), 438 (40), 394 (50), 291 (42), 168 (10), 57 (100); ^{1}H NMR: $\delta = 1.16$ (9H, s, C(CH$_3$)$_3$), 1.43 (3H, t, $J = 7.1$ Hz, CH$_3$), 1.50 (9H, s, C(CH$_3$)$_3$), 1.52 (3H, t, $J = 7$ Hz, CH$_3$), 4.41 (2H, q, $J = 7.1$ Hz, CH$_2$), 4.83 (1H, s, CH), 4.88 and 4.93 (2H, 2dq, $^2J_{HH} = 10.3$ Hz, $^3J_{HH} = 7$ Hz, AMX$_3$ system, CHOCH$_2$CH$_3$), 7.43 (1H, d, $J = 7.3$ Hz, CH), 7.52 (1H, t, $J = 7.6$ Hz, CH), 7.59 (1H, t, $J = 7.9$ Hz, CH), 7.83 (1H, d, $J = 8.2$ Hz, CH), 7.95 (1H, d, $J = 7.4$ Hz, CH), 8.34 (1H, d, $J = 7.8$ Hz, CH), 9.47 (1H, s, NH) ppm; ^{13}C NMR: $\delta = 13.98$ and 15.71 (2 CH$_3$), 27.64 and 28.22 (2 C(CH$_3$)$_3$), 63.97 and 65.36 (2 OCH$_2$), 68.77 (OCH), 82.07 and 83.01 (2 CMe$_3$), 115.29 (N–C=C), 122.33 (C), 122.47, 123.89, 125.76, 126.39, 127.47 (5 CH), 129.70 (C), 130.35 (CH), 130.66, 136.09, 154.07 (3 C), 154.87, 160.48, 160.84, 165.98, 166.35 (5 C=O) ppm.

Dimethyl-4-ethoxy-1-(8-((2-ethoxy-2-oxoacetyl)-amino)-1-naphthyl)-5-oxo-4,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**3b**; C$_{24}$H$_{24}$N$_2$O$_9$)

3b-I: colorless crystals; m.p.: 178–180°C; IR (KBr): $\nu = 3255$ (N–H), 1711 (C=O) cm^{-1}; MS: m/z (%) = 484 (M$^+$, 31), 452 (100), 420 (25), 393 (25), 351 (25), 320 (28), 291 (58), 263 (63), 235 (15), 207 (20), 167 (45), 140 (18), 59 (20); ^{1}H NMR: $\delta = 1.46$ and 1.49 (6H, 2t, $J = 7.1$ Hz, 2 CH$_3$), 3.55 and 3.83 (6H, 2s, 2 OCH$_3$), 4.47 (2H, m, ABX$_3$ system, OCH$_2$CH$_3$), 4.77 and 4.96 (2H, 2dq, $^2J_{HH} = 10.3$ Hz, $^3J_{HH} = 7$ Hz, AMX$_3$ system, CHOCH$_2$CH$_3$), 5.54 (1H, s, CH), 7.36 (1H, d, $J = 7.4$ Hz, CH), 7.57 (1H, t, $J = 7.6$ Hz, CH), 7.67 (1H, t, $J = 7.9$ Hz, CH), 7.87 (1H, d, $J = 7.5$ Hz, CH), 7.98 (1H, d, $J = 7.5$ Hz, CH), 8.08 (1H, d, $J = 7.3$ Hz, CH), 10.47 (1H, s, NH) ppm; ^{13}C NMR: $\delta = 13.92$ and 15.73 (2 CH$_3$), 52.07, 53.64 (2 OCH$_3$), 63.26, 64.34 (2 OCH$_2$CH$_3$), 68.63 (OCH), 112.67 (N–C=C), 125.03 (C), 125.42, 125.43, 126.43, 127.02, 127.74 (5 CH), 130.09 (C), 130.88 (CH), 130.94, 136.13, 153.68 (3 C), 154.97, 161.06, 162.27, 165.88, 169.04 (5 C=O) ppm.

    3b-II (uncrystallized isomer): ^{1}H NMR: $\delta = 1.43$ and 1.53 (6H, 2t, $J = 7.1$ Hz, 2 CH$_3$), 3.48 and 3.76 (6H, 2s, 2 OCH$_3$), 4.47 (2H, m, ABX$_3$ system, OCH$_2$CH$_3$), 4.88 and 4.96 (2H, 2dq, $^2J_{HH} = 10.3$ Hz, $^3J_{HH} = 7$ Hz, AMX$_3$ system, CHOCH$_2$CH$_3$), 5.01 (1H, s, CH), 7.35 (1H, d, $J = 7.3$ Hz, CH), 7.51 (1H, t, $J = 8$ Hz, CH), 7.58 (1H, t, $J = 8$ Hz, CH), 7.83 (1H, d, $J = 7.1$ Hz, CH), 7.95 (1H, d, $J = 7.6$ Hz, CH), 8.25 (1H, d, $J = 7.6$ Hz, CH), 9.61 (1H, s, NH) ppm; ^{13}C NMR: $\delta = 13.84$, 14.07

(2 CH$_3$), 51.97, 52.81 (2 OCH$_3$), 63.97, 64.14 (2 OCH$_2$CH$_3$), 69.00 (OCH), 112.60 (N−C=C), 123.26 (C), 124.14, 125.49, 125.81, 127.87, 129.47 (5 CH), 129.95 (C), 130.86 (CH), 130.92, 136.17, 154.23 (3 C), 155.17, 161.93, 161.77, 165.88, 167.79 (5 C=O) ppm.

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