Ph_3P-Mediated Tandem Synthesis of Functionalized Cyclopentadienes from Primary Alkylamines and Acetylenic Esters

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Abstract: Dialkyl 4-[alkyl(alkoxycarbonyl)amino]-3-alkoxy-1,3-cyclopentadiene-1,2-dicarboxylates are obtained in good yields via a tandem reaction between triphenylphosphine, primary alkylamines, and acetylenic esters in dichloromethane in the absence of catalyst.

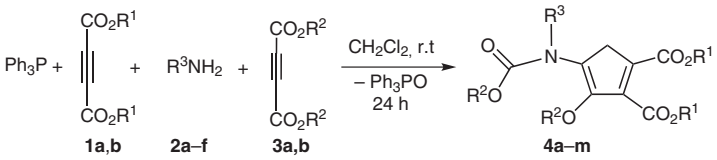
Key words: primary alkylamine, acetylenic ester, 1,3-cyclopentadiene, tandem reaction

Tandem reactions that require in situ generation of reactive species are a special type of organic reaction in which the products are formed by sequential reactions[1–5] and can lead to skeletal changes rather than merely functional-group transformations when the subsequent reaction for which the structural prerequisite is absent in the initial substrate is triggered by the first reaction.

As part of our current studies on the development of new multicompnenent reactions to synthesize novel functional carbocycles and heterocycles,[6–9] we report herein a facile one-pot synthesis of dialkyl 3-alkoxy 4-[alkyl(alkoxycarbonyl)amino]-1,3-cyclopentadiene-1,2-dicarboxylates **4** via the reaction between triphenylphosphine, dialkyl acetylenedicarboxylates **1** and **3**, and primary alkylamines **2** in CH_2Cl_2 at room temperature in good yields[10] (Table 1).

The structures of compounds **4** were assigned on the basis of spectroscopic data. The ^1H NMR and ^{13}C NMR spectra of the crude products clearly indicated the formation of di-

Table 1 Reaction of Ph_3P, Acetylenic Esters, and Primary Alkylamines



1a,b 2a–f 3a,b 4a–m

Acetylenedicarboxylate **1**		Amine **2**		Acetylenedicarboxylate **3**		Product **4**	Yield (%)
	R^1		R^3		R^2		
1a	Me	**2a**	$C_6H_5CH_2$	**3a**	Me	**4a**	71
1a	Me	**2b**	4-$MeC_6H_4CH_2$	**3a**	Me	**4b**	78
1a	Me	**2c**	4-$MeOC_6H_4CH_2$	**3a**	Me	**4c**	80
1a	Me	**2d**	2-$ClC_6H_4CH_2$	**3a**	Me	**4d**	65
1a	Me	**2e**	1-$C_{10}H_7CH_2$	**3a**	Me	**4e**	62
1a	Me	**2f**	*n*-Bu	**3a**	Me	**4f**	67
1b	Et	**2a**	$C_6H_5CH_2$	**3b**	Et	**4g**	59
1b	Et	**2a**	$C_6H_5CH_2$	**3a**	Me	**4h**	75
1b	Et	**2c**	4-$MeOC_6H_4CH_2$	**3a**	Me	**4i**	77
1b	Et	**2d**	2-$ClC_6H_4CH_2$	**3a**	Me	**4j**	73
1b	Et	**2e**	1-$C_{10}H_7CH_2$	**3a**	Me	**4k**	63
1b	Et	**2f**	*n*-Bu	**3a**	Me	**4l**	69
1a	Me	**2a**	$C_6H_5CH_2$	**3b**	Et	**4m**	67

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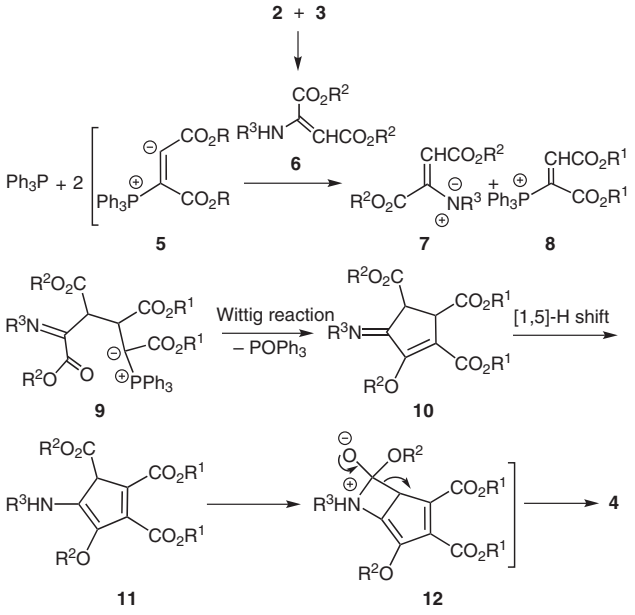
alkyl 3-alkoxy 4-[alkyl(alkoxycarbonyl)amino]-1,3-cyclopentadiene-1,2-dicarboxylates **4** with no other product other being identified in the reaction mixture.

The ^{1}H NMR spectrum of **4a** exhibited six sharp singlets readily recognized as arising from methylene (δ = 3.52 and 5.50 ppm) and methoxy (δ = 3.58, 3.76, 3.84, and 3.89 ppm) protons along with characteristic resonances for the phenyl group. The ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the proposed structure. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**m** are similar to those for **4a**, except for the alkyl and ester groups, which showed characteristic signals in appropriate regions of the spectra. The mass spectra of compounds **4** displayed molecular ion peaks at appropriate *m/z* values.

Although the mechanistic details of the reaction have not been elucidated, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterionic intermediate **5**, generated from Ph_3P and acetylenic ester **1**, is trapped by the enaminoester **6**, generated in situ from the corresponding alkylamine **2** and acetylenic ester **3**,[11] to produce intermediates **7** and **8** (Table 1). Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to an adduct **9**, which undergoes intramolecular Wittig reaction to afford imino-cyclopentene derivative **10**. Intermediate **10** undergoes a [1,5]-H shift to generate **11**, which is converted to **4** via the bicyclic tetrahedral intermediate **12**.



Scheme 1 A proposed mechanism of the reaction

According to this mechanism, the formation of a single product when two different alkynes are used (Table 1, compounds **4h**–**m**), is presumably controlled by the sequence in which the reaction is carried out. When the ethyl and methyl substituents of the acetylenedicarboxylates are reversed, two different products **4h** and **4m** were obtained. This result supports the proposed mechanism shown in Scheme 1.

In conclusion, we have reported the synthesis of highly functionalized cyclopenta-1,3-dienes via a tandem reaction between Ph_3P, primary alkylamines, and dialkyl acetylenedicarboxylates in CH_2Cl_2. This tandem protocol may be considered as a practical route for the synthesis of functionalized 1,3-cyclopentadine ring systems.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **Compounds 4a–g – General Procedure**
To a stirred solution of amine **2** (2 mmol) and the acetylenic ester (4 mmol) in CH_2Cl_2 (10 mL), was added Ph_3P (0.53 g, 2 mmol) at 0 °C, and the mixture was allowed to reach r.t. After completion of the reaction (6–12 h; TLC monitoring, EtOAc–hexane = 1:4), the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–400 mesh; Merck), hexane–EtOAc = 5:1): pure product.
Dimethyl 4-[Benzyl(methoxycarbonyl)amino]-3-methoxy-1,3-cyclopentadiene-1,2-dicarboxylate (4a)
Yellow oil; yield 0.53 g (71%). IR (KBr): ν_{max} = 1732, 1707, 1625, 1560, 1506, 1451, 1409, 1282, 1248, 1151, 1090, 742, 687 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.52 (2 H, s, CH_2), 3.58, 3.76, 3.84, 3.89 (12 H, s, 4 MeO), 5.50 (2 H, s, CH), 6.97 (2 H, d, ^3J = 7.8 Hz, CH), 7.25–7.32 (3 H, m, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.3 (CH_2), 48.8, 51.8, 52.0, 52.2 (4 MeO), 63.0 (CH_2N), 113.6 (C), 120.1 (C), 121.0 (C), 125.9 (2 CH), 127.4 (CH), 128.7 (2 CH), 136.7 (C), 143.9 (C), 161.0 (COO), 164.9 (COO), 169.5 (COO) ppm. MS: *m/z* (%) = 376 (7) [M$^+$ + 1], 375 (22) [M$^+$], 361 (4), 344 (10), 311 (11), 284 (5), 91 (75), 77 (21), 59 (11). Anal. Calcd for $C_{19}H_{21}NO_7$ (375.37): C, 60.80; H, 5.64; N, 3.73. Found: C, 61.1; H, 5.7; N, 3.7.
Compounds 4h–m – General Procedure
To a stirred solution of amine **2** (2 mmol) and the first acetylenic ester (2 mmol) in CH_2Cl_2 (10 mL), was simultaneously added Ph_3P (0.52 g, 2 mmol) and the second acetylenic ester (2 mmol) at 0 °C. The mixture was then allowed to reach r.t. After completion of the reaction (6–12 h; TLC monitoring, EtOAc–hexane = 1:4), the solvent was evaporated, and the residue was purified by column

chromatography [silica gel (230–400 mesh; Merck), hexane–EtOAc = 5:1]: pure product.

Diethyl 4-[Benzyl(methoxycarbonyl)amino]-3-methoxy-1,3-cyclopentadiene-1,2-dicarboxylate (4h)

Pale yellow oil; yield 0.60 g (75%). IR (KBr): ν_{max} = 1735, 1704, 1629, 1596, 1503, 1452, 1416, 1280, 1247, 1150, 1094, 744, 693 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.26 (3 H, t, ^3J = 7.1 Hz, Me), 1.38 (3 H, t, ^3J = 7.1 Hz, Me), 3.52 (2 H, s, CH_2), 3.58, 3.85 (6 H, s, 2 MeO), 4.22 (2 H, q, ^3J = 7.1 Hz, CH_2O), 4.36 (2 H, q, ^3J = 7.1 Hz, CH_2O), 5.50 (2 H, s, CH_2N), 6.98 (2 H, d, ^3J = 7.3 Hz, CH), 7.25 (1 H, t, ^3J = 7.2 Hz, CH), 7.31 (2 H, t, ^3J = 7.2 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 14.1 (Me), 28.9 (CH_2), 48.7, 52.2 (2 MeO), 60.8, 60.9 (2 OCH_2), 63.0 (CH_2N), 114.0 (C), 120.1 (C), 120.8 (C), 125.9 (2 CH), 127.4 (CH), 128.6 (2 CH), 136.8 (C), 143.7 (C), 160.6 (COO), 164.5 (COO), 169.6 (COO) ppm. MS: *m/z* (%) = 404 (12) [M^+ + 1], 403 (28) [M^+], 389 (4), 372 (6), 325 (13), 312 (5), 91 (75), 77 (25), 73 (16), 59 (12). Anal. Calcd for $C_{21}H_{25}NO_7$ (403.42): C, 62.52; H, 6.25; N, 3.47. Found: C, 62.4; H, 6.3; N, 3.5.

Dimethyl 4-[Benzyl(ethoxycarbonyl)amino]-3-ethoxy-1,3-cyclopentadiene-1,2-dicarboxylate (4m)

Pale yellow oil; yield 0.54 g (67%). IR (KBr): ν_{max} = 1738, 1714, 1630, 1590, 1513, 1458, 1421, 1291, 1247, 1155, 1099, 745, 690 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (3 H, t, ^3J = 7.1 Hz, Me), 1.30 (3 H, t, ^3J = 7.1 Hz, Me), 3.49 (2 H, s, CH_2), 3.76, 3.87 (6 H, s, 2 MeO), 4.02 (2 H, q, ^3J = 7.1 Hz, CH_2O), 4.04 (2 H, q, ^3J = 7.1 Hz, CH_2O), 5.50 (2 H, s, CH_2N), 6.94 (2 H, d, ^3J = 7.3 Hz, CH), 7.23 (1 H, t, ^3J = 7.2 Hz, CH), 7.28 (2 H, t, ^3J = 7.2 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 15.3 (Me), 29.6 (CH_2), 48.8, 51.9 (2 MeO), 52.0, 61.3 (2 OCH_2), 71.5 (CH_2N), 114.5 (C), 121.1 (C), 121.8 (C), 125.9 (2 CH), 127.4 (CH), 128.7 (2 CH), 135.8 (C), 144.7 (C), 161.5 (COO), 163.4 (COO), 168.5 (COO) ppm. MS: *m/z* (%) = 404 (8) [M^+ + 1], 403 (17) [M^+], 389 (4), 372 (6), 325 (11), 91 (70), 77 (22), 73 (12), 59 (9). Anal. Calcd for $C_{21}H_{25}NO_7$ (403.42): C, 62.52; H, 6.25; N, 3.47. Found: C, 62.7; H, 6.4; N, 3.6.

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